Fig. 1

```
   1 MTSLMLLLLLFAFVQPCASIVEKRCGPIDIRNRPWDIKPQWSKLGDPNEKDLAGQRMVNCT
  61 VVEGSLTISFVLKHKTKAQEEMHRSLQPRYSQDEFITFPHLREITGTLLVFETEGLVDLR
 121 KIFPNLRVIGGRSLIQHYALIIYRNPDLEIGLDKLSVIRNGGVRIIDNRKLCYTKTIDWK
 181 HLITSSINDVVVDNAAEYAVTETGLMCPRGACEEDKGESKCHYLEEKNQEQGVERVQSCW
 241 SNTTCQKSCAYDRLLPTKEIGPGCDANGDRCHDQCVGGCERVNDATACHACKNVYHKGKC
 301 IEKCDAHLYLLLQRRCVTREQCLQLNPVLSNKTVPIKATAGLCSDKCPDGYQINPDDHRE
 361 CRKCVGKCEIVCEINHVIDTFPKAQAIRLCNIIDGNLTIEIRGKQDSGMASELKDIFANI
 421 HTITGYLLVRQSSPFISLNMFRNLRRIEAKSLFRNLYAITVFENPNLKKLFDSTTDLTLD
 481 RGTVSIANNKMLCFKYIKQLMSKLNIPLDPIDQSEGTNGEKAICEDMAINVSITAVNADS
 541 VFFSWPSFNITDIDQRKFLGYELFFKEVPRIDENMTIEEDRSACVDSWQSVFKQYYETSN
 601 GEPTPDIFMDIGPRERIRPNTLYAYYVATQMVLHAGAKNGVSKIGFVRTSYYTPDPPTLA
 661 LAQVDSDAIHITWEAPLQPNGDLTHYTIMWRENEVSPYEEAEKFCTDASTPANRQRTKDP
 721 KETIVADKPVDIPSSRTVAPTLLTMMGHEDQQKTCAATPGCCSCSAIEESSEQNKKKRPD
 781 PMSAIESSAFENKLLDEVLMPRDTMRVRRSIEDANRVSEELEKAENLGKAPKTLGGKKPL
 841 IHISKKKPSSSSTTSTPAPTIASMYALTRKPTTVPGTRIRLYEIYEPLPGSWAINVSALA
 901 LDNSYVIRNLKHYTLYAISLSACQNMTVPGASCSISHRAGALKRTKHITDIDKVLNETIE
 961 WRFMNNSQQVNVTWDPPTEVNGGIFGYVVKLKSKVDGSIVMTRCVGAKRGYSTRNQGVLF
1021 QNLADGRYFVSVTATSVHGAGPEAESSDPIVVMTPGFFTVEIILGMLLVFLILMSIAGCI
1081 IYYYIQVRYGKKVKALSDFMQLNPEYCVDNKYNADDWELRQDDVVLGQQCGEGSFGKVYL
1141 GTGNNVVSLMGDRFGPCAIKINVDDPASTENLNYLMEANIMKNFKTNFIVQLYGVISTVQ
1201 PAMVVMEMMDLGNLRDYLRSKREDEVFNETDCNFFDIIPRDKFHEWAAQICDGMAYLESL
1261 KFCHRDLAARNCMINRDETVKIGDFGMARDLFYHDYYKPSGKRMMPVRWMSPESLKDGKF
1321 DSKSDVWSFGVVLYEMVTLGAQPYIGLSNDEVLNYIGMARKVIKKPECCENYWYKVMKMC
1381 WRYSPRDRPTFLQLVHLIAAEASPEFRDLSFVLTDNQMILDDSEALDLDDIDDTDMNDQV
1441 VEVAPDVENVEVQSDSERRNTDSIPLKQFKTIPPINATTSHSTISIDETPMKAKQREGSL
1501 DEEYALMNHSGGPSDAEVRTYAGDGDYVERDVRENDVPTRRNTGASTSSYTGGGPYCLTN
1561 RGGSNERGAGFGEAVRLTDGVGSGHLNDDDYVEKEISSMDTRRSTGASSSSYGVPQTNWS
1621 GNRGATYYTSKAQQAATAAAAAAALQQQQNGGRGDRLTQLPGTGHLQSTRGGQDGDYIE
1681 TEPKNYRNNGSPSRNGNSRDIFNGRSAFGENEHLIEDNEHHPLV
```

Fig. 2A

```
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  51 ttctactgta ctccccgaaa aaccaacaaa aaacacaagt ttttgaacac
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 151 agacgacaca aaattttgga aaatttggaa gaagagaatc tcggcccgag
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```

Fig. 2B (sheet 1 of 3)

```
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2951   aaaagctgaa   aatttgggaa   aagctccaaa   aactctcggt   ggaaagaagc
3001   cgctgatcca   tatttcgaag   aagaagccgt   cgagcagcag   caccacatcc
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5101   cgcgacgaaa   tactggtgca   tcaacatcaa   gttacacagg   tggtggtcca
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Fig. 2B (sheet 2 of 3)

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5701  cccacattat catatctcta cacgaatatc ggattttttt tcagattttt
5751  tctgaaaaat tctgaataat tttaccccat ttttcaaatc tctgtatttt
5801  tttttgttat tacccc
```

Fig. 2B (sheet 3 of 3)

Fig. 2C (sheet 1 of 2)

ligand-binding

100 aa

IRS-1-like

Insulin/IGF-I receptor

Drosophila

DAF-2

cys

36(35)% 24(26)% 24(22)% 50(49)%
33% 22% 24% 48%

IGF-IR
InR
DInR
DAF-2

L(e1368)T(e1365)
Y(mg43)
L(mg43)
S(sa187)
N(sa229)

Insulin/IGF-I receptor

Drosophila

DAF-2

100 aa

IRS-1-like

tyrosine kinase

cys 36(35)% | 24(26)% | 24(22)% | 50(49)%

cys 33% | 22% | 24% | 48%

cys

```
IGF-IR  ALPVAVLIVGGLVIMLYVFHRKRN.NSRLGNGVLYASVNPEYF SAAD.....VIVVPDLWEVAREKITMSRELGQGSFGMVYEGVAKGVVKDEPET..RV
InR     IGPLIFVFLFSVVIGSIYLFLRKRQPDGPL...GPLYASSNPEYLSASDVFPCSVYVPDLWEVSREKITLLRELGQGSFGMVYEGNARDIIKGEAET..RV
DInR    GIGLAFIV..SLFGYVCYLHKRKVPSNDLY.HMNTEVNPFYASMQ.......YIPDDWEVLRENIIQLAPLGQGSFGMVYECILKSFPPNGVDR..EC
DAF-2   GMLLVELILMSIAGCILYYIQVLYY.GKKVKALSDFMQLNPLYCVDNK.....YNADDWELRQEDLMVLGQQCGEGSFGKVYLGTGNNVVSLMGDRFGPC

IGF-IR  AIKTVNLEAANSMRERIELFLNLEASVMKLEFNCHHVVRLLGVVSLQGQPTLVLMELMTRGDLKSYLRSLRPEMENNPVLA.........PPSLSKMIQMAGE
InR     AMKTVNESASLRERIELFLNLEASVMKGFTCHHVVRLLGVVSKGQPTLVVMELMAHGDLKSYLRSLRPEAAENNPGRP.........PPTLQEMIQMAAE
DInR    AIKTVNENATDRERTNELSEASVMKLEFDTYHVVRLLGVCSRGQPALVVMELMLKKGDLKSYLRAHRPEERDEAAMTYLNRIGVTGNVQPPTYGRIYQMAIE
DAF-2   ALKINVEDDPASTENLNIIMEANLMNEKTNFIWVQLYGVISTVQLPAIVVWEIDLGNLLILDYLRSKREKEVFNETDCNFFDIIPR......DKFHEWWAAQ

IGF-IR  IADGMAYLNANKFVHRDLAARNCMVAEDFTVKIGDFGMTRDIYETDYYRKGGKGLLPVRWMSPESLKDGVFTTYSDVWSFGVVLWEIATLAEQPYQGLSN
InR     IADGMAYLNAKKFVHRDLAARNCMVAHDFTVKIGDFGMTRDIYETDYYRKGGKGLLPVRWMAPESLKDGVFTTSSDMWSFGVVLWEITSLAEQPYQGLSN
DInR    IADGMAYLAAKKFVHRDLAARNCWADDLTVKIGDFGMTRDIYETDYYRKCTKGLLPVRWMPPESLKDGVFSSASDVFSFGVVLWEMATLAAQPYQGLSN
DAF-2   ICDGMAYLESLKFCHRDLAARNCMFNRDETVKIGDFGMARDLIYHDYYRPSGKRMPVRWMSPESLKDGKFDSKSDVWSFGVVLWIEMVLLGAQPYIGLSN

IGF-IR  EQVLRFV.MEGGLLDKPDNCPDMLFELMRMCWQYNPKMRPSFLEIISSLKEE.MEPGFREVSFYYSE...ENKLPEPEELDLEPENMESVPLDPS......
InR     EQVLKFV.MDGGYLDQPDNCPERVTDLMRMCWQFNPKMRPTFLEIVNLLKDD.LHPSFPEVSFFHSE...ENKAPESELEMEFEDMENVPLDRS......
DInR    EQVLRYW.IDCGVMERPENCPDFLHKLMQRCWHHRSSARPSFLDIIAYLEPQCPNSQFKEVSFYHSEAGLQHREKERKERN.QLDAFAAAVPLDQDLQDRE
DAF-2   REVLNVAGMARKVIKKPECCENYWYKVMKCWRYSEPRDRPTFLQEVHLLAAE.ASPERRLSFVLTD...NQMILDDSEALDLDDIDDTDMNDQVVEVA
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N(sa219)   TE   E   I   Q   L   Q   V   S

L(e1391)   L(e1370)   S(e1370)
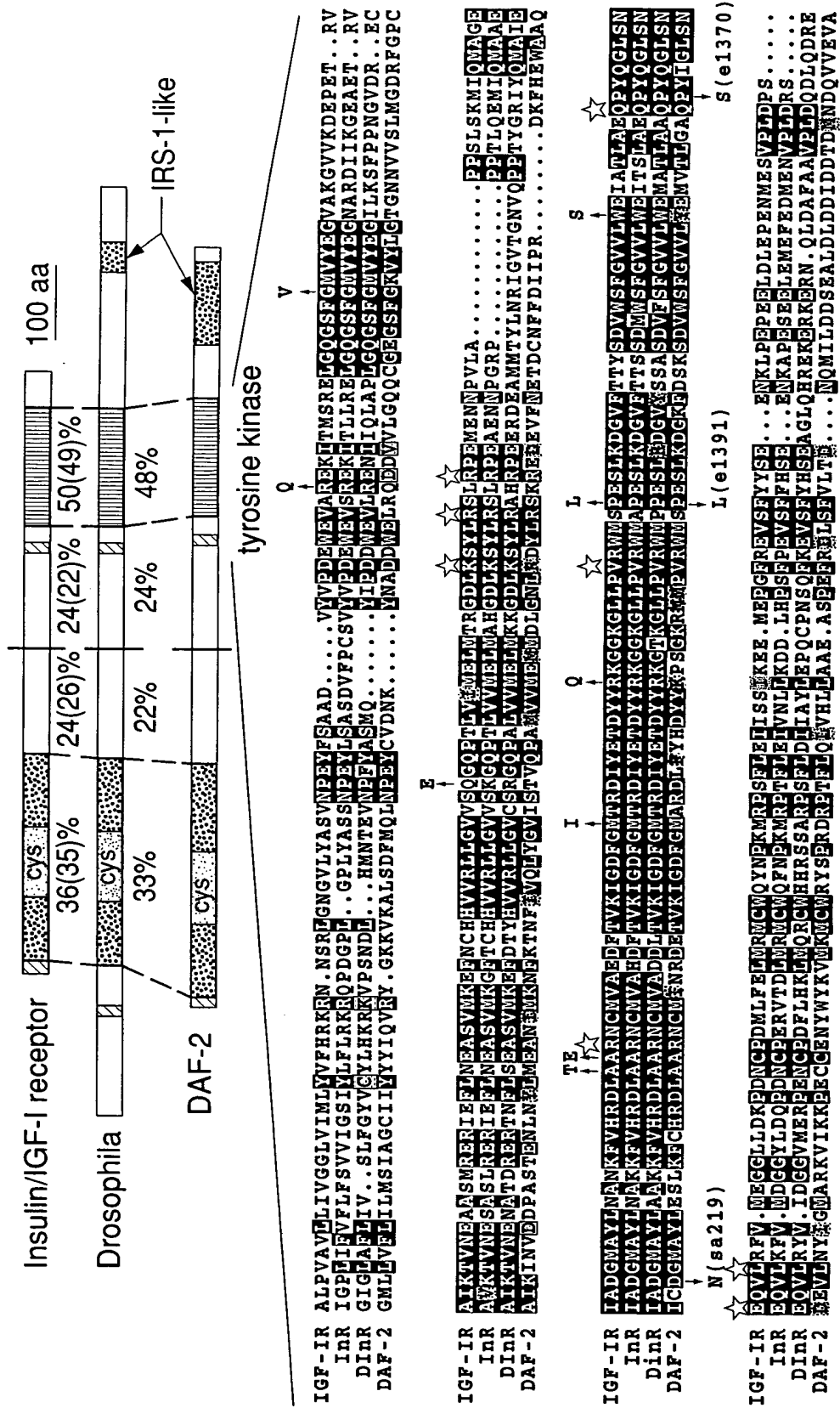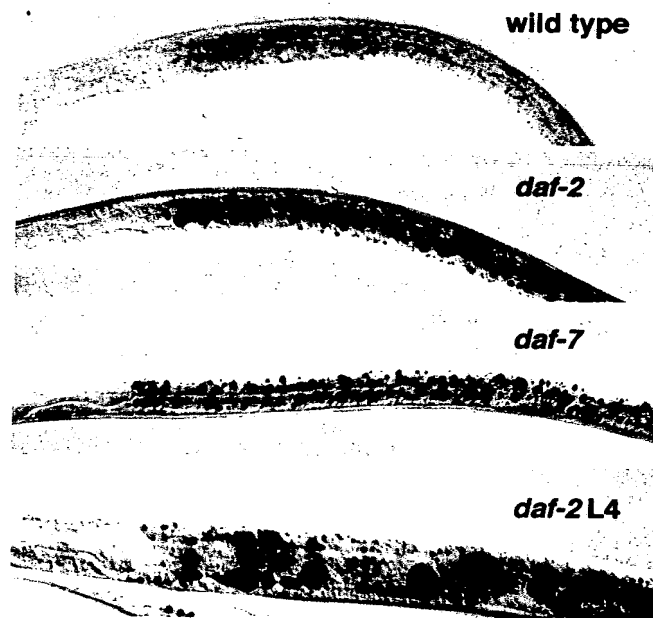
Fig. 2C (sheet 2 of 2)

Fig. 3

Fig. 4

Fig. 5A
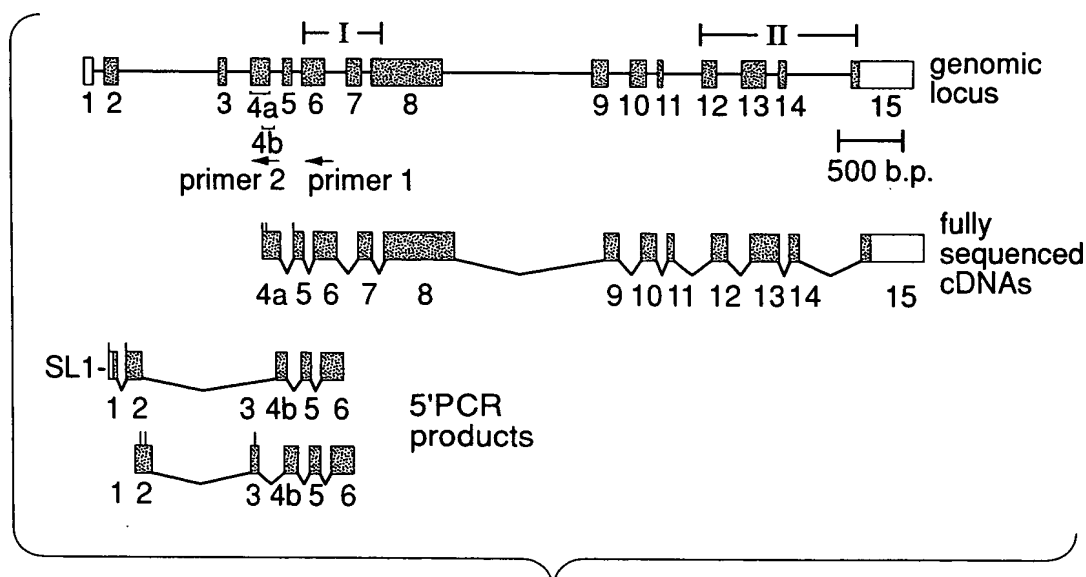
Fig. 5B

Domain I

```
DAF-3    .NIDREFDQKACESLVKKLKDKKNDLQNLIDVVLSKGTKYTGCITIPRTLDG
          |    | ||||||||| || || |  | ||     |   | || |||||
DPC4     GGESETFAKRAIESLVKKLKEKKDELDSLITAITTNGAHPSKCVTIQRTLDG
             mg125 P->L
         RLQVHGRKGFPHVVYGKLWRFNEMTKNETRHVDHCKHAFEMKSDMVCVNPYH
         |||| ||||||||| |  |||      |||  ||  |  ||  | | |||||||||
         RLQVAGRKGFPHVIYARLWRWPDLHKNELKHVKYCQYAFDLKCDSVCVNPYH
```

Domain II

```
DAF-3    IVYYEKNLQIGE..KKCSRGNFHVDGGFI..CSENRYSLGLEPNPIREPVAFKV
         | | |    | || |   |        |        | || |  | |
DPC4     IAYFEMDVQVGETFKVPSSCPIVTVDGYVDPSGGDRFCLGQLSNVHRTEAIERA
             mg132   G->E
         RKAIVDGIRFSYKKDGSVWLQNRMKYPVFVTSGYLDEQSGGLKKDKVHKVYGCA
         | |    | |   | | |||        ||| | |||     |   | ||| | |
         RLHIGKGVQLECKGEGDVWVRCLSDHAVFVQSYYLDREAGRAPGDAVHKIYPSA

         SIKTFGFNVSKQIIRDALLSKQMA....TMYLQGKLTPMNYIYEKKTQEELRRE
          ||  |   | | ||        | |         | |              |
         YIKVFDLRQCHRQMQQQAATAQAAAAAQAAAVAGNIPGPGSVGGIAPAISLSAA

         ATRTTDSLAKYCCVRVSFCKGFGEAYPERPSIHDCPVWIELKINIAYDFMD
         |    | || | || ||| ||||  ||||| |||||  |||     |  |
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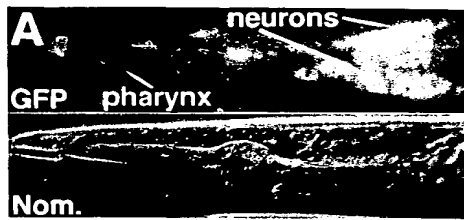
Fig. 5C
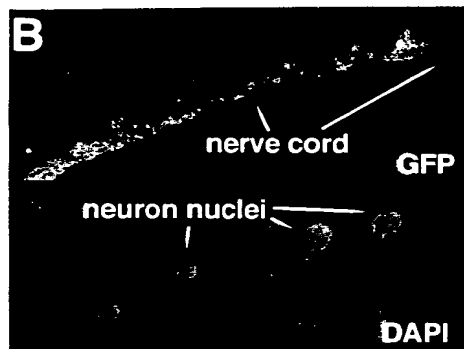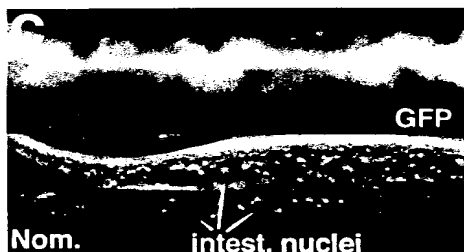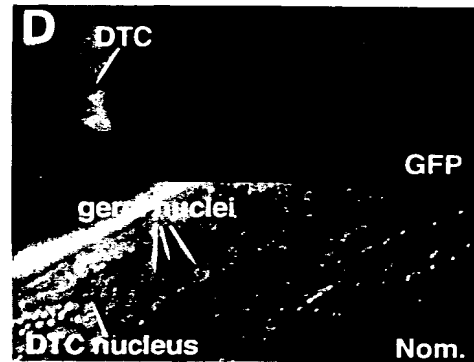
Fig. 6A

Fig. 6B

Fig. 6C

Fig. 6D

Fig. 6E

Fig. 6F

Fig. 6G

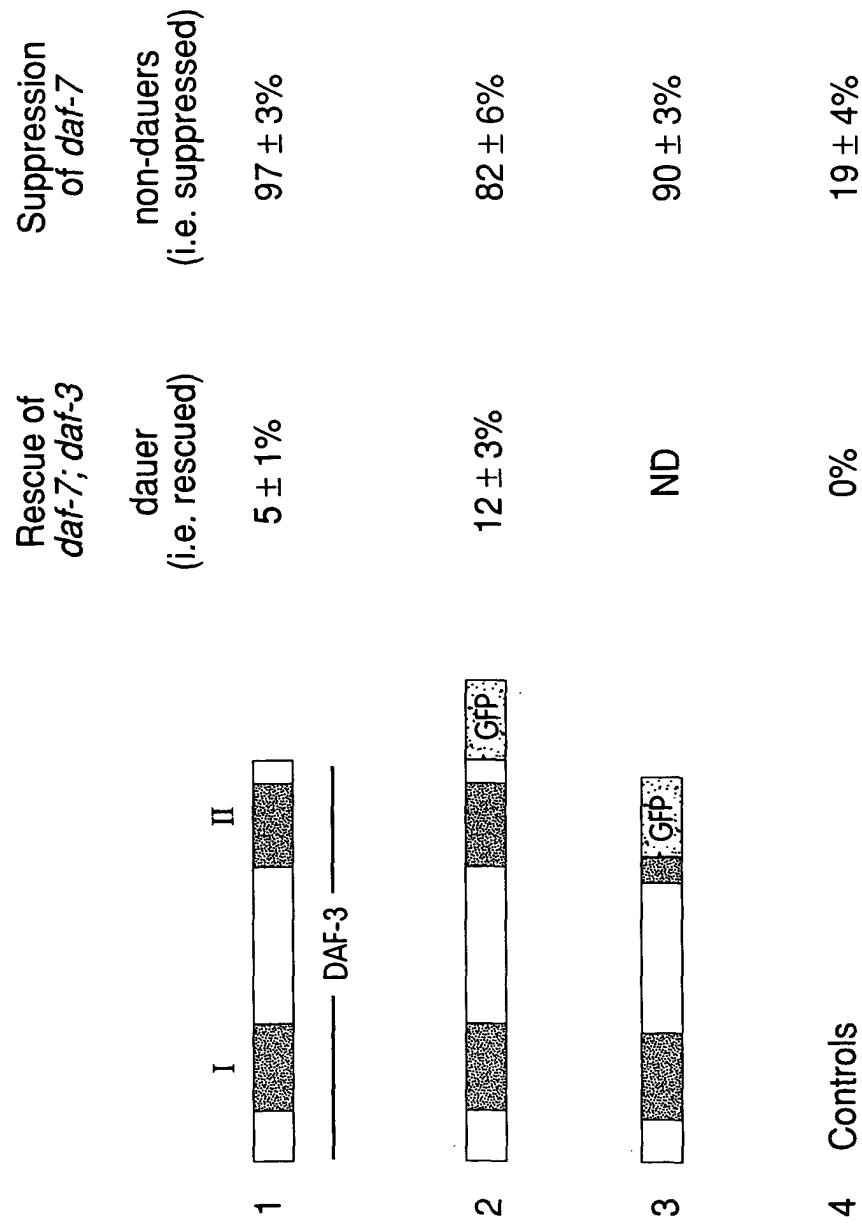|		Rescue of daf-7; daf-3	Suppression of daf-7
		dauer (i.e. rescued)	non-dauers (i.e. suppressed)
1	I II — DAF-3 —	5 ± 1%	97 ± 3%
2	GFP	12 ± 3%	82 ± 6%
3	GFP	ND	90 ± 3%
4	Controls	0%	19 ± 4%
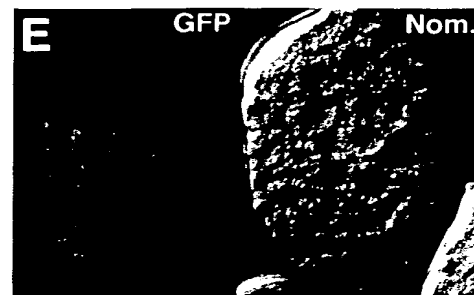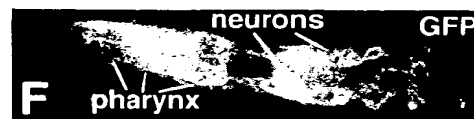
Fig. 7

Fig. 8A
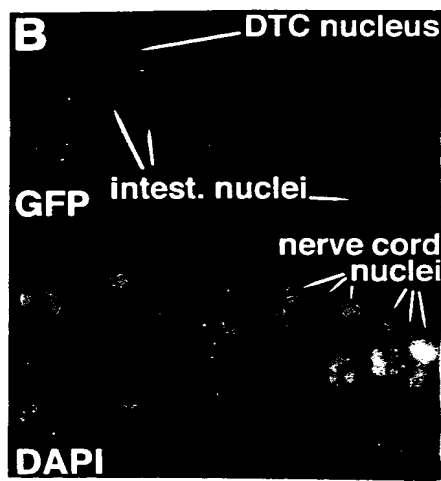
Fig. 8B
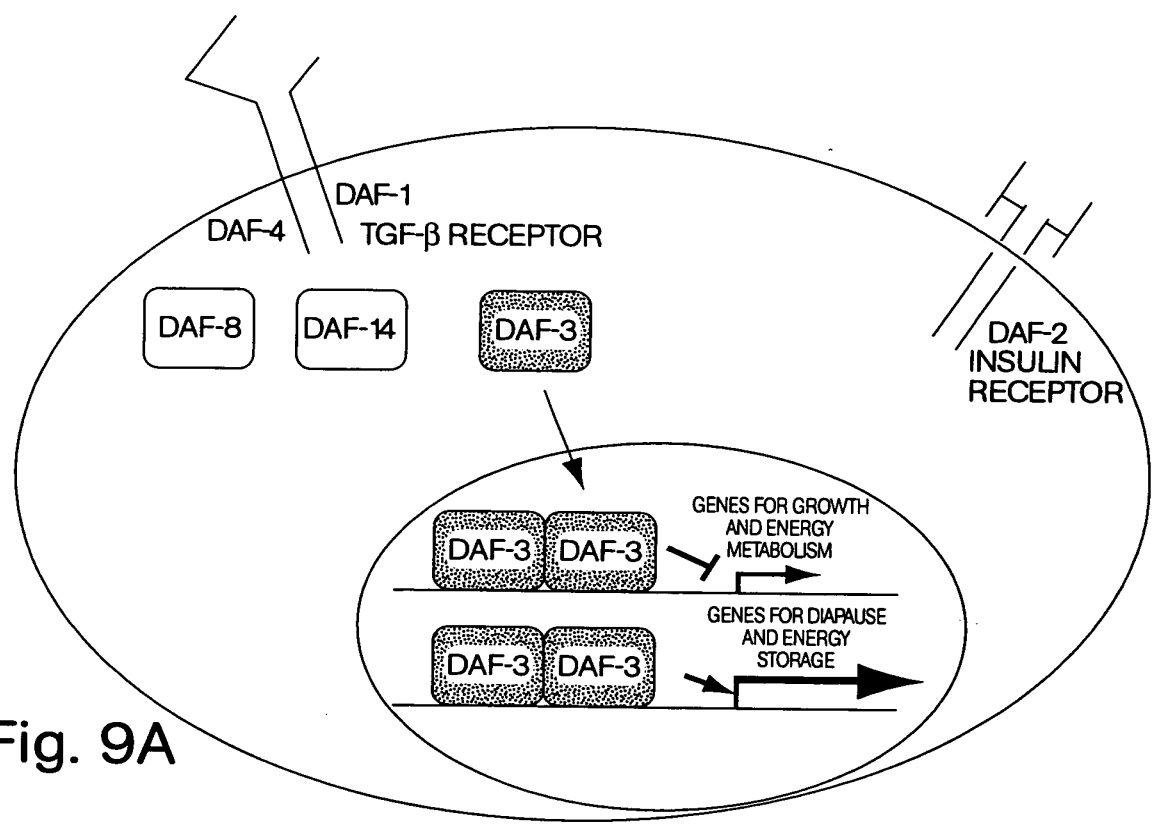
Fig. 9A
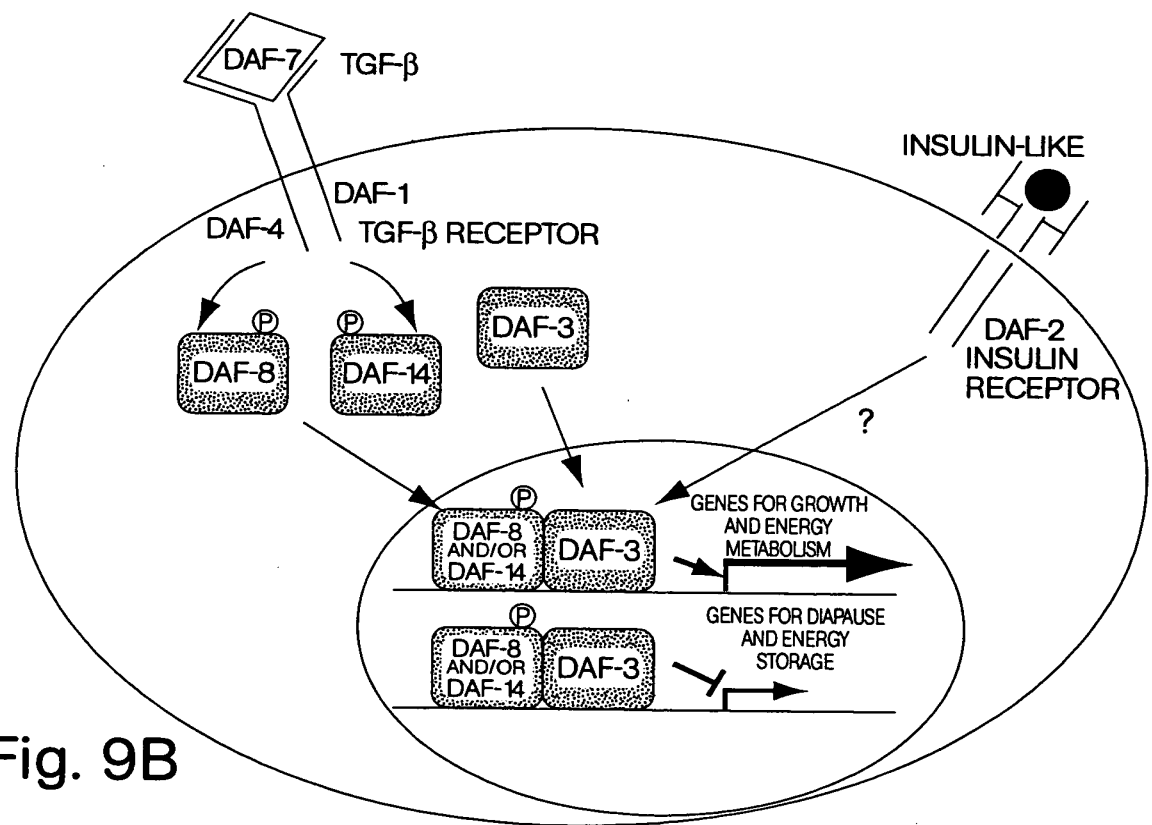
Fig. 9B
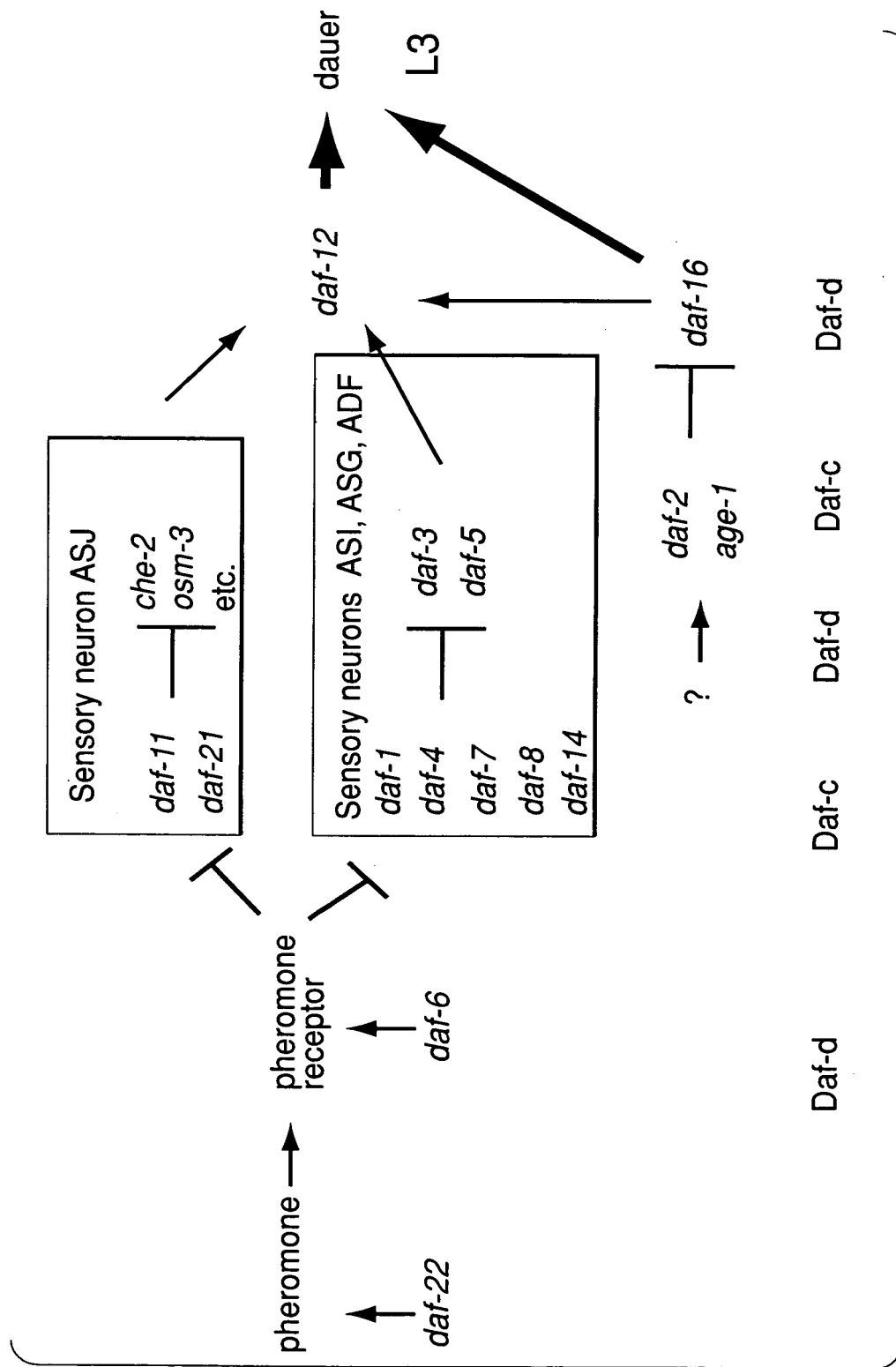
Fig. 10

```
   1  atgaagctaa tagcaacttc tcttctagtt cccgacgagc acacaccgat
  51  gatgtcacca gtgaatacaa ctacaaagat tctacaacgg agtggtatta
 101  aaatggaaat cccgccatat ttggatccag acagtcagga tgatgacccg
 151  gaagatggtg tcaactaccc ggatccagat ttatttgaca caaaaaacac
 201  aaatatgacc gagtacgatt tggatgtgtt gaagcttgga aaaccagcag
 251  tagatgaagc acggaaaaag atcgaagttc ccgacgctag tgcgccgcca
 301  aacaaaattg tagaatattt gatgtattat agaacgttaa aagaaagtga
 351  actcatacaa ctgaatgcgt atcggacaaa acgaaatcga ttatcgttga
 401  acttggtcaa aaacaatatt gatcgagagt tcgaccaaaa agcttgcgag
 451  tccctggtga aaaaattgaa ggataagaag aatgatctcc agaacctgat
 501  tgatgtggtt cttttcaaaag gtacaaaata taccggttgc attacaattc
 551  caaggacact tgatggccgg ttacaggtcc acggaagaaa aggtttccct
 601  cacgtagtct atggcaaact gtggaggttt aatgaaatga caaaaaacga
 651  aacgcgtcat gtggaccact gcaagcacgc atttgaaatg aaaagtgaca
 701  tggtatgcgt gaatccctat cactacgaaa ttgtcattgg aactatgatt
 751  gttgggcaga gggatcatga caatcgagat atgccgccgc cacatcaacg
 801  ctaccacact ccaggtcggc aggatccagt tgacgatatg agtagattta
 851  taccaccagc ttccattcgt ccgcctccga tgaacatgca cacaaggcct
 901  cagcctatgc ctcaacaatt gccttcagtt ggcgcaacgt ttgcccatcc
 951  tctcccacat caggcgccac ataacccagg ggtttcacat ccgtactcca
1001  ttgctccaca gacccattac ccgttgaaca tgaacccaat tccgcaaatg
1051  ccgcaaatgc cacaaatgcc accacctctc catcagggat atggaatgaa
1101  tgggccgagt tgctcttcag aaaacaacaa tccattccac caaaatcacc
1151  attataatga tattagccat ccaaatcact attcctacga ctgtggtccg
1201  aacttgtacg ggtttccaac tccttatccg gattttcacc atcctttcaa
1251  tcagcaacca caccagccgc cacaactatc acaaaaccat acgtcccaac
1301  aaggcagtca tcaaccaggg caccaaggtc aggtaccgaa tgatccacca
1351  atttcaagac cagtgttaca accatcaaca gtcaccttgg acgtgttccg
1401  tcggtactgt agacagacat ttggaaatcg attttttgaa ggagaaagtg
1451  aacaatccgg cgcaataatt cggtctagta acaaattcat tgaagaattt
1501  gattcgccga tttgtggtgt gacagttgtt cgaccgcgga tgacagacgg
1551  tgaggttttg gagaacatca tgccggaaga tgcaccatat catgacattt
1601  gcaagttcat tttgaggctc acatcagaaa gtgtaacttt ctcaggagag
1651  gggccagaag ttagtgattt gaacgaaaaa tggggaacaa ttgtgtacta
1701  tgagaaaaat ttgcaaattg gcgagaaaaa atgttcgaga ggaaatttcc
1751  acgtggatgg cggattcatt tgctctgaga atcgttacag tctcggactt
1801  gagccaaatc caattagaga accagtggcg tttaaagttc gtaaagcaat
1851  agtggatgga attcgctttt cctacaaaaa agacgggagt gtttggcttc
1901  aaaaccgcat gaagtacccg gtatttgtca cttctgggta tctcgacgag
1951  caatcaggag gcctaaagaa ggataaagtg cacaaagttt acggatgtgc
2001  gtctatcaaa acgtttggct tcaacgtttc caaacaaatc atcagagacg
2051  cgcttctttc caagcaaatg gcaacaatgt acttgcaagg aaaaattgact
```

Fig. 11A (sheet 1 of 2)

```
2101  ccgatgaatt atatctacga gaagaagact caggaagagc tgcgaaggga
2151  agcaacacgc accactgatt cattggccaa gtactgttgt gtccgtgtct
2201  cgttctgcaa aggatttgga gaagcatacc cagaacgccc gtcaattcat
2251  gattgtccag tttggattga gttgaaaatc aacattgcct acgatttcat
2301  ggattcaatc tgccagtaca taaccaactg cttcgagccg ctaggaatgg
2351  aagattttgc aaaattggga atcaacgtca gtgatgacta aatgataact
2401  tttttcactc accctactag atactgattt agtcttattc caaatcatcc
2451  aacgatatca aactttttcc tttgaacttt gcatactatg ttatcacaag
2501  ttccaagcag tttcaataca aacataggat atgttaacaa cttttgataa
2551  gaatcaagtt accaactgtt cattgtgagc tttgagctgt atagaaggac
2601  aatgtatccc atacctcaat ctttaatagt catcagtcac tggtcccgca
2651  ccaatttttt cgattcgcat atgtcatata ttgcaccgtg gcccttttta
2701  ttgtaacttt taatatattt tcttcccaac ttgtgaatat gattgatgaa
2751  ccaccatttt gagtaataaa tgtatttttt gtgg
```

Fig. 11A (sheet 2 of 2)

```
   1  gtaatcaaat tgtaaaggaa aaatattaat agtcagagta cacataaatg
  51  ggtgatcatc ataatttaac gggccttccc ggtacctcca tcccgccaca
 101  gttcaactat tctcagcccg gtaccagcac cggaggcccg ctttatggtg
 151  gaaaaccttc tcatggattg gaagatattc ctgatgtaga ggaatatgag
 201  aggaacctgc tcggggctgg agcaggtttt aatctgctca atgtaggaaa
 251  tatggctaat gttcccgacg agcacacacc gatgatgtca ccagtgaata
 301  caactacaaa gattctacaa cggagtggta ttaaaatgga aatcccgcca
 351  tatttggatc cagacagtca ggatgatgac ccggaagatg gtgtcaacta
 401  cccggatcca gatttatttg acacaaaaaa cacaaatatg accgagtacg
 451  atttggatgt gttgaagctt ggaaaaccag cagtagatga agcacggaaa
 501  aagatcgaag ttcccgacgc tagtgcgccg ccaaacaaaa ttgtagaata
 551  tttgatgtat tatagaacgt taaagaaag tgaactcata caactgaatg
 601  cgtatcggac aaaacgaaat cgattatcgt tgaacttggt caaaaacaat
 651  attgatcgag agttcgacca aaaagcttgc gagtccctgg tgaaaaaatt
 701  gaaggataag aagaatgatc tccagaacct gattgatgtg gttctttcaa
 751  aaggtacaaa atataccggt tgcattacaa ttccaaggac acttgatggc
 801  cggttacagg tccacggaag aaaaggtttc cctcacgtag tctatggcaa
 851  actgtggagg tttaatgaaa tgacaaaaaa cgaaacgcgt catgtggacc
 901  actgcaagca cgcatttgaa atgaaaagtg acatggtatg cgtgaatccc
 951  tatcactacg aaattgtcat tggaactatg attgttgggc agagggatca
1001  tgacaatcga gatatgccgc cgccacatca acgctaccac actccaggtc
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1851  ctcacatcag aaagtgtaac tttctcagga gaggggccag aagttagtga
1901  tttgaacgaa aaatggggaa caattgtgta ctatgagaaa aatttgcaaa
1951  ttggcgagaa aaaatgttcg agaggaaatt tccacgtgga tggcggattc
2001  atttgctctg agaatcgtta cagtctcgga cttgagccaa atccaattag
2051  agaaccagtg gcgtttaaag ttcgtaaagc aatagtggat ggaattcgct
```

Fig. 11B (sheet 1 of 2)

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2201  gaaggataaa gtgcacaaag tttacggatg tgcgtctatc aaaacgtttg
2251  gcttcaacgt ttccaaacaa atcatcagag acgcgcttct ttccaagcaa
2301  atggcaacaa tgtacttgca aggaaaattg actccgatga attatatcta
2351  cgagaagaag actcaggaag agctgcgaag ggaagcaaca cgcaccactg
2401  attcattggc caagtactgt tgtgtccgtg tctcgttctg caaaggattt
2451  ggagaagcat acccagaacg cccgtcaatt catgattgtc cagtttggat
2501  tgagttgaaa atcaacattg cctacgattt catggattca atctgccagt
2551  acataaccaa ctgcttcgag ccgctaggaa tggaagattt tgcaaaattg
2601  ggaatcaacg tcagtgatga ctaaatgata acttttttca ctcaccctac
2651  tagatactga tttagtctta ttccaaatca tccaacgata tcaaactttt
2701  tcctttgaac tttgcatact atgttatcac aagttccaag cagtttcaat
2751  acaaacatag gatatgttaa caacttttga taagaatcaa gttaccaact
2801  gttcattgtg agctttgagc tgtatagaag gacaatgtat cccatacctc
2851  aatctttaat agtcatcagt cactggtccc gcaccaattt tttcgattcg
2901  catatgtcat atattgcacc gtggcccttt ttattgtaac ttttaatata
2951  ttttcttccc aacttgtgaa tatgattgat gaaccaccat tttgagtaat
3001  aaatgtattt tttgtgg
```

Fig. 11B (sheet 2 of 2)

```
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 201  aggaacctgc  tcggggctgg  agcaggtttt  aatctgctca  atgtaggaaa
 251  tatggctaat  gaatttaaac  caataatcac  attggacacg  aaaccacctc
 301  gtgatgccaa  caagtcattg  gcattcaatg  gcgggttgaa  gctaatcact
 351  ccgaaaactg  aagttcccga  cgagcacaca  ccgatgatgt  caccagtgaa
 401  tacaactaca  aagattctac  aacggagtgg  tattaaaatg  gaaatcccgc
 451  catatttgga  tccagacagt  caggatgatg  acccggaaga  tggtgtcaac
 501  tacccggatc  cagatttatt  tgacacaaaa  aacacaaata  tgaccgagta
 551  cgatttggat  gtgttgaagc  ttggaaaacc  agcagtagat  gaagcacgga
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1801  taattcggtc  tagtaacaaa  ttcattgaag  aatttgattc  gccgatttgt
1851  ggtgtgacag  ttgttcgacc  gcggatgaca  gacggtgagg  ttttggagaa
1901  catcatgccg  gaagatgcac  catatcatga  catttgcaag  ttcattttga
1951  ggctcacatc  agaaagtgta  actttctcag  gagaggggcc  agaagttagt
2001  gatttgaacg  aaaaatgggg  aacaattgtg  tactatgaga  aaaatttgca
2051  aattggcgag  aaaaaatgtt  cgagaggaaa  tttccacgtg  gatggcggat
```

Fig. 11C (sheet 1 of 2)

```
2101  tcatttgctc tgagaatcgt tacagtctcg gacttgagcc aaatccaatt
2151  agagaaccag tggcgtttaa agttcgtaaa gcaatagtgg atggaattcg
2201  cttttcctac aaaaaagacg ggagtgtttg gcttcaaaac cgcatgaagt
2251  acccggtatt tgtcacttct gggtatctcg acgagcaatc aggaggccta
2301  aagaaggata aagtgcacaa agtttacgga tgtgcgtcta tcaaaacgtt
2351  tggcttcaac gtttccaaac aaatcatcag agacgcgctt ctttccaagc
2401  aaatggcaac aatgtacttg caaggaaaat tgactccgat gaattatatc
2451  tacgagaaga agactcagga agagctgcga agggaagcaa cacgcaccac
2501  tgattcattg gccaagtact gttgtgtccg tgtctcgttc tgcaaaggat
2551  ttggagaagc atacccagaa cgcccgtcaa ttcatgattg tccagtttgg
2601  attgagttga aaatcaacat tgcctacgat ttcatggatt caatctgcca
2651  gtacataacc aactgcttcg agccgctagg aatggaagat tttgcaaaat
2701  tgggaatcaa cgtcagtgat gactaaatga taactttttt cactcaccct
2751  actagatact gatttagtct tattccaaat catccaacga tatcaaactt
2801  tttcctttga actttgcata ctatgttatc acaagttcca agcagtttca
2851  atacaaacat aggatatgtt aacaactttt gataagaatc aagttaccaa
2901  ctgttcattg tgagctttga gctgtataga aggacaatgt atcccatacc
2951  tcaatcttta atagtcatca gtcactggtc ccgcaccaat tttttcgatt
3001  cgcatatgtc atatattgca ccgtggccct ttttattgta acttttaata
3051  tattttcttc ccaacttgtg aatatgattg atgaaccacc attttgagta
3101  ataaatgtat tttttgtgg
```

Fig. 11C (sheet 2 of 2)

```
  1   MKLIATSLLV  PDEHTPMMSP  VNTTTKILQR  SGIKMEIPPY  LDPDSQDDDP
 51   EDGVNYPDPD  LFDTKNTNMT  EYDLDVLKLG  KPAVDEARKK  IEVPDASAPP
101   NKIVEYLMYY  RTLKESELIQ  LNAYRTKRNR  LSLNLVKNNI  DREFDQKACE
151   SLVKKLKDKK  NDLQNLIDVV  LSKGTKYTGC  ITIPRTLDGR  LQVHGRKGFP
201   HVVYGKLWRF  NEMTKNETRH  VDHCKHAFEM  KSDMVCVNPY  HYEIVIGTMI
251   VGQRDHDNRD  MPPPHQRYHT  PGRQDPVDDM  SRFIPPASIR  PPPMNMHTRP
301   QPMPQQLPSV  GATFAHPLPH  QAPHNPGVSH  PYSIAPQTHY  PLNMNPIPQM
351   PQMPQMPPPL  HQGYGMNGPS  CSSENNNPFH  QNHHYNDISH  PNHYSYDCGP
401   NLYGFPTPYP  DFHHPFNQQP  HQPPQLSQNH  TSQQGSHQPG  HQGQVPNDPP
451   ISRPVLQPST  VTLDVFRRYC  RQTFGNRFFE  GESEQSGAII  RSSNKFIEEF
501   DSPICGVTVV  RPRMTDGEVL  ENIMPEDAPY  HDICKFILRL  TSESVTFSGE
551   GPEVSDLNEK  WGTIVYYEKN  LQIGEKKCSR  GNFHVDGGFI  CSENRYSLGL
601   EPNPIREPVA  FKVRKAIVDG  IRFSYKKDGS  VWLQNRMKYP  VFVTSGYLDE
651   QSGGLKKDKV  HKVYGCASIK  TFGFNVSKQI  IRDALLSKQM  ATMYLQGKLT
701   PMNYIYEKKT  QEELRREATR  TTDSLAKYCC  VRVSFCKGFG  EAYPERPSIH
751   DCPVWIELKI  NIAYDFMDSI  CQYITNCFEP  LGMEDFAKLG  INVSDD
```

Fig. 12A

```
  1 MGDHHNLTGL PGTSIPPQFN YSQPGTSTGG PLYGGKPSHG LEDIPDVEEY
 51 ERNLLGAGAG FNLLNVGNMA NVPDEHTPMM SPVNTTTKIL QRSGIKMEIP
101 PYLDPDSQDD DPEDGVNYPD PDLFDTKNTN MTEYDLDVLK LGKPAVDEAR
151 KKIEVPDASA PPNKIVEYLM YYRTLKESEL IQLNAYRTKR NRLSLNLVKN
201 NIDREFDQKA CESLVKKLKD KKNDLQNLID VVLSKGTKYT GCITIPRTLD
251 GRLQVHGRKG FPHVVYGKLW RFNEMTKNET RHVDHCKHAF EMKSDMVCVN
301 PYHYEIVIGT MIVGQRDHDN RDMPPPHQRY HTPGRQDPVD DMSRFIPPAS
351 IRPPPMNMHT RPQPMPQQLP SVGATFAHPL PHQAPHNPGV SHPYSIAPQT
401 HYPLNMNPIP QMPQMPQMPP PLHQGYGMNG PSCSSENNNP FHQNHHYNDI
451 SHPNHYSYDC GPNLYGFPTP YPDFHHPFNQ QPHQPPQLSQ NHTSQQGSHQ
501 PGHQGQVPND PPISRPVLQP STVTLDVFRR YCRQTFGNRF FEGESEQSGA
551 IIRSSNKFIE EFDSPICGVT VVRPRMTDGE VLENIMPEDA PYHDICKFIL
601 RLTSESVTFS GEGPEVSDLN EKWGTIVYYE KNLQIGEKKC SRGNFHVDGG
651 FICSENRYSL GLEPNPIREP VAFKVRKAIV DGIRFSYKKD GSVWLQNRMK
701 YPVFVTSGYL DEQSGGLKKD KVHKVYGCAS IKTFGFNVSK QIIRDALLSK
751 QMATMYLQGK LTPMNYIYEK KTQEELRREA TRTTDSLAKY CCVRVSFCKG
801 FGEAYPERPS IHDCPVWIEL KINIAYDFMD SICQYITNCF EPLGMEDFAK
851 LGINVSDD
```

Fig. 12B

```
  1 MGDHHNLTGL PGTSIPPQFN YSQPGTSTGG PLYGGKPSHG LEDIPDVEEY
 51 ERNLLGAGAG FNLLNVGNMA NEFKPIITLD TKPPRDANKS LAFNGGLKLI
101 TPKTEVPDEH TPMMSPVNTT TKILQRSGIK MEIPPYLDPD SQDDDPEDGV
151 NYPDPDLFDT KNTNMTEYDL DVLKLGKPAV DEARKKIEVP DASAPPNKIV
201 EYLMYYRTLK ESELIQLNAY RTKRNRLSLN LVKNNIDREF DQKACESLVK
251 KLKDKKNDLQ NLIDVVLSKG TKYTGCITIP RTLDGRLQVH GRKGFPHVVY
301 GKLWRFNEMT KNETRHVDHC KHAFEMKSDM VCVNPYHYEI VIGTMIVGQR
351 DHDNRDMPPP HQRYHTPGRQ DPVDDMSRFI PPASIRPPPM NMHTRPQPMP
401 QQLPSVGATF AHPLPHQAPH NPGVSHPYSI APQTHYPLNM NPIPQMPQMP
451 QMPPPLHQGY GMNGPSCSSE NNNPFHQNHH YNDISHPNHY SYDCGPNLYG
501 FPTPYPDFHH PFNQQPHQPP QLSQNHTSQQ GSHQPGHQGQ VPNDPPISRP
551 VLQPSTVTLD VFRRYCRQTF GNRFFEGESE QSGAIIRSSN KFIEEFDSPI
601 CGVTVVRPRM TDGEVLENIM PEDAPYHDIC KFILRLTSES VTFSGEGPEV
651 SDLNEKWGTI VYYEKNLQIG EKKCSRGNFH VDGGFICSEN RYSLGLEPNP
701 IREPVAFKVR KAIVDGIRFS YKKDGSVWLQ NRMKYPVFVT SGYLDEQSGG
751 LKKDKVHKVY GCASIKTFGF NVSKQIIRDA LLSKQMATMY LQGKLTPMNY
801 IYEKKTQEEL RREATRTTDS LAKYCCVRVS FCKGFGEAYP ERPSIHDCPV
851 WIELKINIAY DFMDSICQYI TNCFEPLGME DFAKLGINVS DD
```

Fig. 12C

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tcactttccccaaaaaccgttcaagctgctgccttcactctcatcccctcctcttactccttcttttctcgtccgctacta
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Fig. 13B

MMEMLVDQGTDASSSASTSTSSVSRFGADTFMNTPDDVMMNDDMEPIPRDR
CNTWPMRRPQLEPPLNSSPIIHEQIPEEDADLYGSNEQCGQLGGASSNGST
AMLHTPDGSNSHQTSFPSDFRMSESPDDTVSGKKTTTRRNAWGNMSYAELI
TTAIMASPEKRLTLAQVYEWMVQNVPYFRDKGDSNSSAGWKNSIRHNLSLH
SRFMRIQNEGAGKSSWWVINPDAKPGMNPRRTRERSNTIETTTKAQLEKSR
RGAKKRIKERALMGSLHSTLNGNSIAGSIQTISHDLYDDDSMQGAFDNVPS
SFRPRTQSNLSIPGSSSRVSPAIGSDIYDDLEFPSWVGESVPAIPSDIVDR
TDQMRIDATTHIGGVQIKQESKPIKTEPIAPPPSYHELNSVRGSCAQNPLL
RNPIVPSTNFKPMPLPGAYGNYQNGGITPINWLSTSNSSPLPGIQSCGIVA
AQHTVASSSALPIDLENLTLPDQPLMDTMDVDALIRHELSQAGGQHIHFDL

Fig. 14A

MQQYIYQESSATIPHHHLNQHNNPYHPMHPHHQLPHMQQLPQPLLNLNMTT
LTSSGSSVASSIGGGAQCSPCASGSSTAATNSSQQQQTVGQMLAASVPCSS
SGMTLGMSLNLSQGGGPMPAKKKRCRKKPTDQLAQKKPNPWGEESYSDIIA
KALESAPDGRLKLNEIYQWFSDNIPYFGERSSPEEAAGWKNSIRHNLSLHS
RFMRIQNEGAGKSSWWVINPDAKPGMNPRRTRERSNTIETTTKAQLEKSRR
GAKKRIKERALMGSLHSTLNGNSIAGSIQTISHDLYDDDSMQGAFDNVPSS
FRPRTQSNLSIPGSSSRVSPAIGSDIYDDLEFPSWVGESVPAIPSDIVDRT
DQMRIDATTHIGGVQIKQESKPIKTEPIAPPPSYHELNSVRGSCAQNPLLR
NPIVPSTNFKPMPLPGAYGNYQNGGITPINWLSTSNSSPLPGIQSCGIVAA
QHTVASSSALPIDLENLTLPDQPLMDTMDVDALIRHELSQAGGQHIHFDL

Fig. 14B

```
   1 cggaagccat ggagctcgag atctgattgc tggacacgga cggaactccg acgtatctcg
  61 cagatgcatg ttaacatttt acatccacaa ctgcaaacga tggtcgagca gtggcaaatg
 121 cgagaacgcc catcgctgga gaccgagaat ggcaaaggat cgctgctcct ggaaaatgaa
 181 ggtgtcgcag atatcatcac tatgtgtcca ttcggagaag ttattagtgt agtatttccg
 241 tggtttcttg caaatgtgcg aacatcgcta gaaatcaagc tatcagattt caaacatcaa
 301 cttttcgaat tgattgctcc gatgaagtgg ggaacatatt ccgtaaagcc acaggattat
 361 gtgttcagac agttgaataa tttcggcgaa attgaagtta tatttaacga cgatcaaccc
 421 ctgtcgaaat tagagctcca cggcactttc ccaatgcttt ttctctacca acctgatgga
 481 ataaacaggg ataaagaatt aatgagtgat ataagtcatt gtctaggata ctcactggat
 541 aaactggaag agagcctcga tgaggaactc cgtcaatttc gtgcttctct ctgggctcgt
 601 acgaagaaaa cgtgcttgac acgtggactt gagggtacca gtcactacgc gttccccgaa
 661 gaacagtact tgtgtgttgg tgaatcgtgc ccgaaagatt tggaatcaaa agtcaaggct
 721 gccaagctga gttatcagat gttttggaga aaacgtaaag cggaaatcaa tggagtttgc
 781 gagaaaatga tgaagattca aattgaattc aatccgaacg aaactccgaa atctctgctt
 841 cacacgtttc tctacgaaat gcgaaaattg gatgtatacg ataccgatga tcctgcagat
 901 gaaggatggt ttcttcaatt ggctggacgt accacgtttg ttacaaatcc agatgtcaaa
 961 cttacgtctt atgatggtgt ccgttcggaa ctggaaagct atcgatgccc tggattcgtt
1021 gttcgccgac aatcactagt cctcaaagac tattgtcgcc caaaaccact ctacgaacca
1081 cattatgtga gagcacacga acgaaaactt gctctagacg tgctcagcgt gtctatagat
1141 agcacaccaa aacagagcaa gaacagtgac atggttatga ctgatttcg tccgacagct
1201 tcactcaaac aagtttcact ttgggacctt gacgcgaatc ttatgatacg gcctgtgaat
1261 atttctggat tcgatttccc ggccgacgtg gatatgtacg ttcgaatcga attcagtgta
1321 tatgtgggga cactgacgct ggcatcaaaa tctacaacaa aagtgaatgc tcaatttgca
1381 aaatggaata aggaaatgta cacttttgat ctatacatga aggatatgcc accatctgca
1441 gtactcagca ttcgtgtttt gtacggaaaa gtgaaattaa aaagtgaaga attcgaagtt
1501 ggttgggtaa atatgtccct aaccgattgg agagatgaac tacgacaagg acaatttta
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1621 aggataggca ccaacgcagc ggttacaatt gaaatctcaa gttatggtgg tagagttcga
1681 atgccgagtc aaggacaata cacatatctc gtcaagcacc gaagtacttg acggaaact
1741 ttgaatatta tgggtgatga ctatgagtcg tgtatcagag atccaggata taagaagctt
1801 cagatgcttg tcaagaagca tgaatctgga attgtattag aggaagatga acaacgtcat
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1921 gaactcgcat ttgtgtggac tgatcgtgag aactttttccg agctctatgt gatgcttgaa
1981 aaatggaaac cgccgagtgt ggcagccgcg ttgactttgc ttggaaaacg ttgcacggat
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2221 tggctgctcc gtgcagagat tgctcgtttg agagattgtg atctgaaaag tgaagaatat
2281 cgccgtatct cacttctgat ggaagcttac ctccgtggaa atgaagagca catcaagatc
2341 atcacccgac aagttgacat ggttgatgag ctcacacgaa tcagcactct tgtcaaagga
2401 atgccaaaag atgttgctac gatgaaactg cgtgacgagc ttcgatcgat tagtcataaa
2461 atggaaaata tggattctcc actggatcct gtgtacaaac tgggtgaaat gataatcgac
2521 aaagccatcg tcctaggaag tgcaaaacgt ccgttaatgc ttcactggaa gaacaaaaat
2581 ccaaagagtg acctgcacct tccgttctgt gcaatgatct tcaagaatgg agacgatctt
2641 cgccaggaca tgcttgttct tcaagttctc gaagttatgg ataacatctg gaaggctgca
```

Fig. 15 (sheet 1 of 2)

```
2701 aacattgatt gctgtttgaa cccgtacgca gttcttccaa tgggagaaat gattggaatt
2761 attgaagttg tgcctaattg taaaacaata ttcgagattc aagttggaac aggattcatg
2821 aatacagcag ttcggagtat tgatccttcg tttatgaata agtggattcg gaaacaatgc
2881 ggaattgaag atgaaaagaa gaaaagcaaa aaggactcta cgaaaaatcc catcgaaaag
2941 aagattgata atactcaagc catgaagaaa tattttgaaa gtgtcgatcg attcctatac
3001 tcgtgtgttg gatattcagt tgccacgtac ataatgggaa tcaaggatcg tcacagtgat
3061 aatctgatgc tcactgaaga tggaaaatat gtccacattg atttcggtca cattttggga
3121 cacggaaaga ccaaacttgg gatccagcga gatcgtcaac cgtttattct aaccgaacac
3181 tttatgacag tgattcgatc gggtaaatct gtggatggaa attcgcatga gctacaaaaa
3241 ttcaaaacgt tatgcgtcga agcctacgaa gtaatgtgga ataatcgaga tttgttcgtt
3301 tccttgttca ccttgatgct cggaatggag ttgcctgagc tgtcgacgaa agcggatttg
3361 gatcatttga agaaaaccct cttctgcaat ggagaaagca aagaagaagc gagaaagttt
3421 ttcgctggaa tctacgaaga agccttcaat ggatcatggt ctaccaaaac gaattggctc
3481 ttccacgcag tcaaacacta ctga
```

Fig. 15 (sheet 2 of 2)

```
   1 RKPWSSRSDC WTRTELRRIS QMHVNILHPQ LQTMVEQWQM RERPSLETEN GKGSLLLENE
  61 GVADIITMCP FGEVISVVFP WFLANVRTSL EIKLSDFKHQ LFELIAPMKW GTYSVKPQDY
 121 VFRQLNNFGE IEVIFNDDQP LSKLELHGTF PMLFLYQPDG INRDKELMSD ISHCLGYSLD
 181 KLEESLDEEL RQFRASLWAR TKKTCLTRGL EGTSHYAFPE EQYLCVGESC PKDLESKVKA
 241 AKLSYQMFWR KRKAEINGVC EKMMKIQIEF NPNETPKSLL HTFLYEMRKL DVYDTDDPAD
 301 EGWFLQLAGR TTFVTNPDVK LTSYDGVRSE LESYRCPGFV VRRQSLVLKD YCRPKPLYEP
 361 HYVRAHERKL ALDVLSVSID STPKQSKNSD MVMTDFRPTA SLKQVSLWDL DANLMIRPVN
 421 ISGFDFPADV DMYVRIEFSV YVGTLTLASK STTKVNAQFA KWNKEMYTFD LYMKDMPPSA
 481 VLSIRVLYGK VKLKSEEFEV GWVNMSLTDW RDELRQGQFL FHLWAPEPTA NRSRIGENGA
 541 RIGTNAAVTI EISSYGGRVR MPSQGQYTYL VKHRSTWTET LNIMGDDYES CIRDPGYKKL
 601 QMLVKKHESG IVLEEDEQRH VWMWRRYIQK QEPDLLIVLS ELAFVWTDRE NFSELYVMLE
 661 KWKPPSVAAA LTLLGKRCTD RVIRKFAVEK LNEQLSPVTF HLFILPLIQA LKYEPRAQSE
 721 VGMMLLTRAL CDYRIGHRLF WLLRAEIARL RDCDLKSEEY RRISLLMEAY LRGNEEHIKI
 781 ITRQVDMVDE LTRISTLVKG MPKDVATMKL RDELRSISHK MENMDSPLDP VYKLGEMIID
 841 KAIVLGSAKR PLMLHWKNKN PKSDLHLPFC AMIFKNGDDL RQDMLVLQVL EVMDNIWKAA
 901 NIDCCLNPYA VLPMGEMIGI IEVVPNCKTI FEIQVGTGFM NTAVRSIDPS FMNKWIRKQC
 961 GIEDEKKKSK KDSTKNPIEK KIDNTQAMKK YFESVDRFLY SCVGYSVATY IMGIKDRHSD
1021 NLMLTEDGKY VHIDFGHILG HGKTKLGIQR DRQPFILTEH FMTVIRSGKS VDGNSHELQK
1081 FKTLCVEAYE VMWNNRDLFV SLFTLMLGME LPELSTKADL DHLKKTLFCN GESKEEARKF
1141 FAGIYEEAFN GSWSTKTNWL FHAVKHY
```

Fig. 16

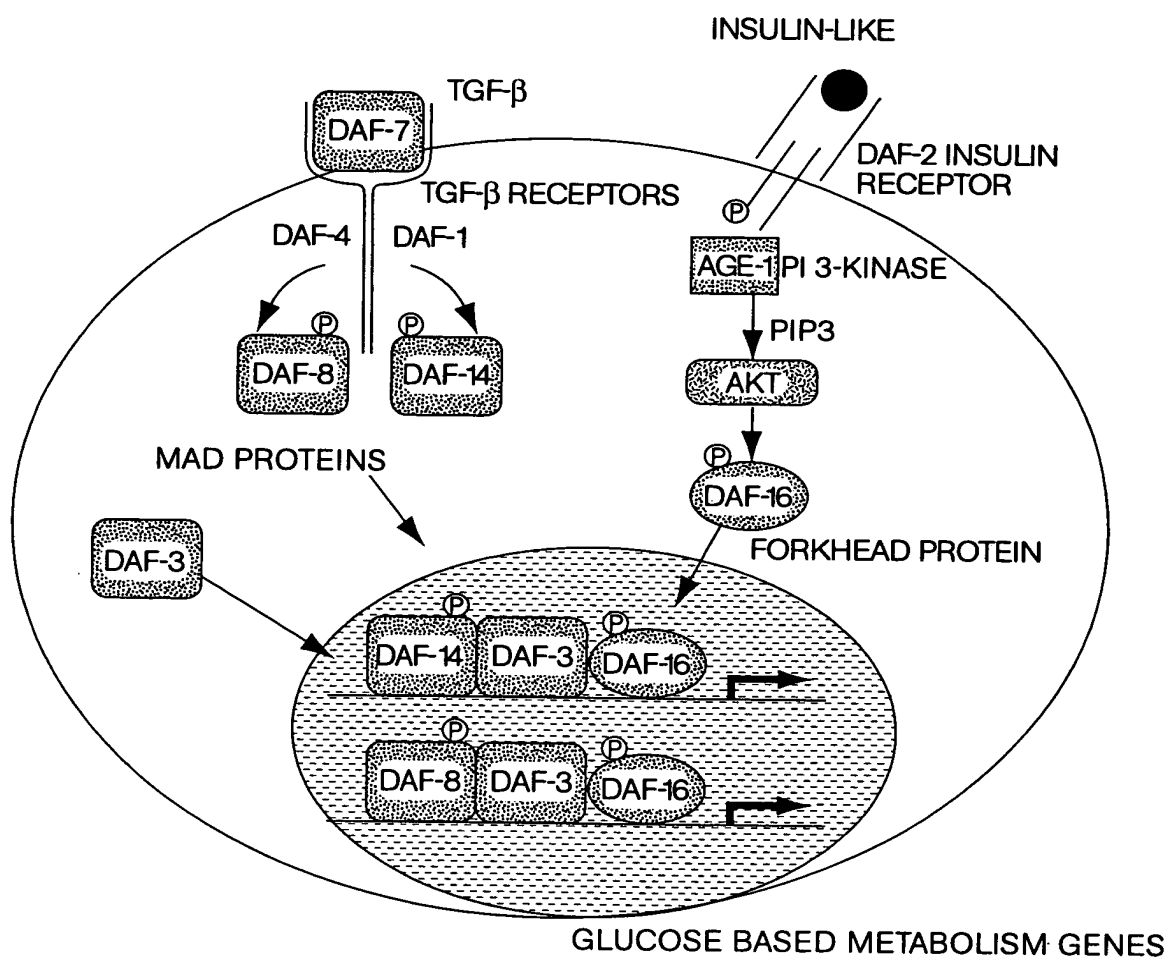# CONVERGENT TGF-β AND INSULIN SIGNALING ACTIVATE GLUCOSE-BASED METABOLISM GENES

Fig. 17

IN PHEROMONE, NO TGFβ OR INSULIN-LIKE SIGNALS
CAUSES REPRESSION OF ANABOLIC GENES

REPRESS GLUCOSE BASED METABOLISM GENES
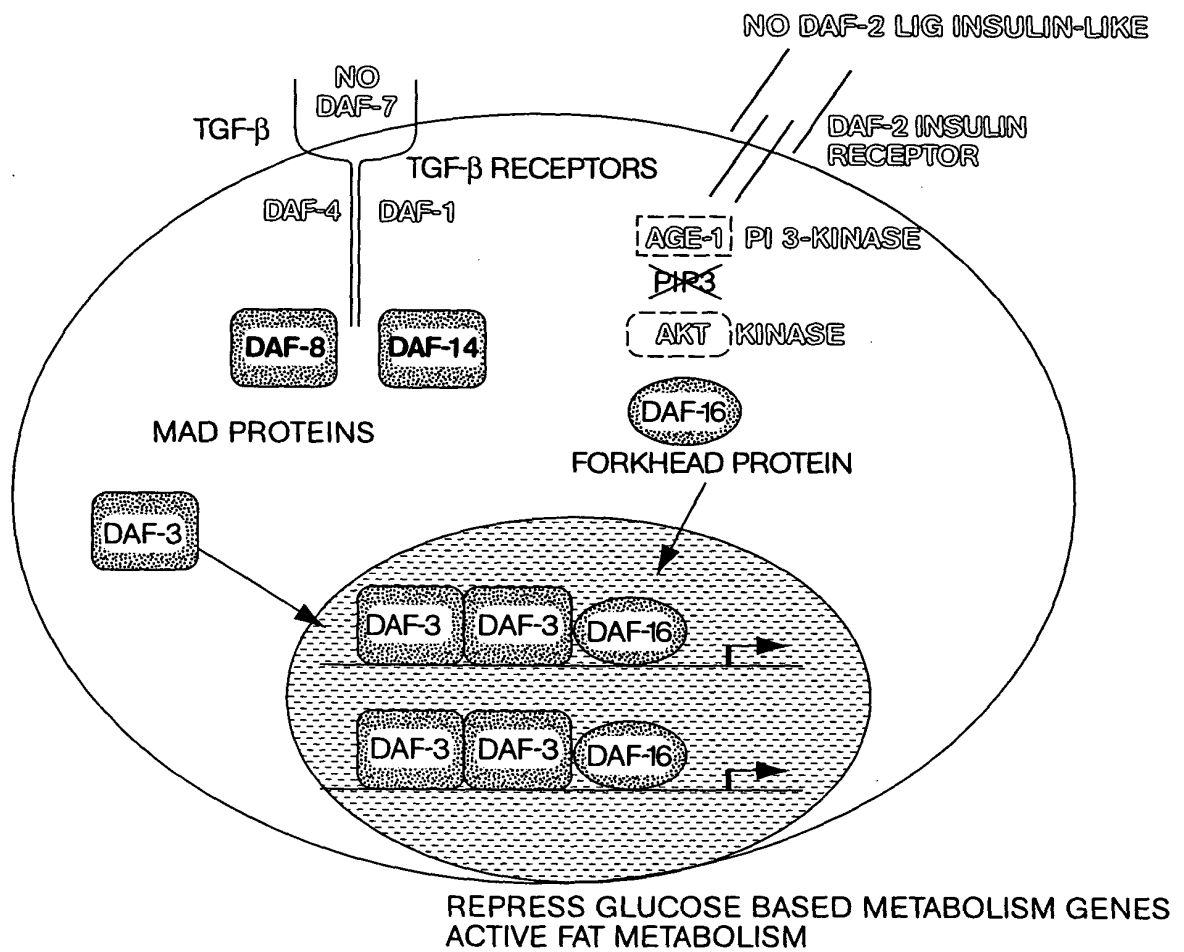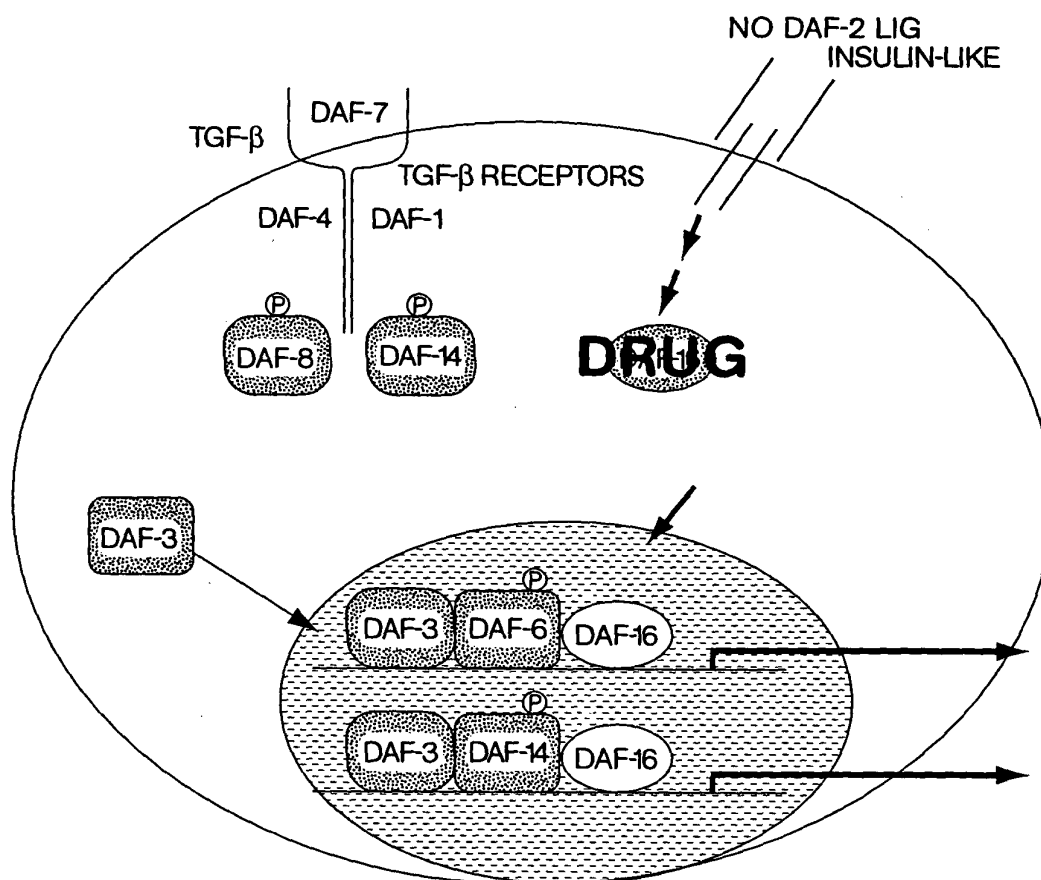ACTIVE FAT METABOLISM

Fig. 18

DRUGS THAT INHIBIT DAF-16 OR DAF-3
(OR PROTEINS IN THE PATHWAY)
CAN BE DISCOVERED USING REPORTER GENES
BEARING THEIR COGNATE BINDING SITES

DRUG CAUSES A DECREASE IN DAF-16 ACTIVITY, ACTIVATING
THE REPORTER GENE LIKE A DAF-16 MUTANT.
THIS BYPASSES THE NEED FOR INSULIN

Fig. 19

**DRUGS THAT INHIBIT DAF-3 WILL CURE
THE DIABETES CAUSED BY A LACK OF DAF-7**

GLUCOSE BASED METABOLISM GENES
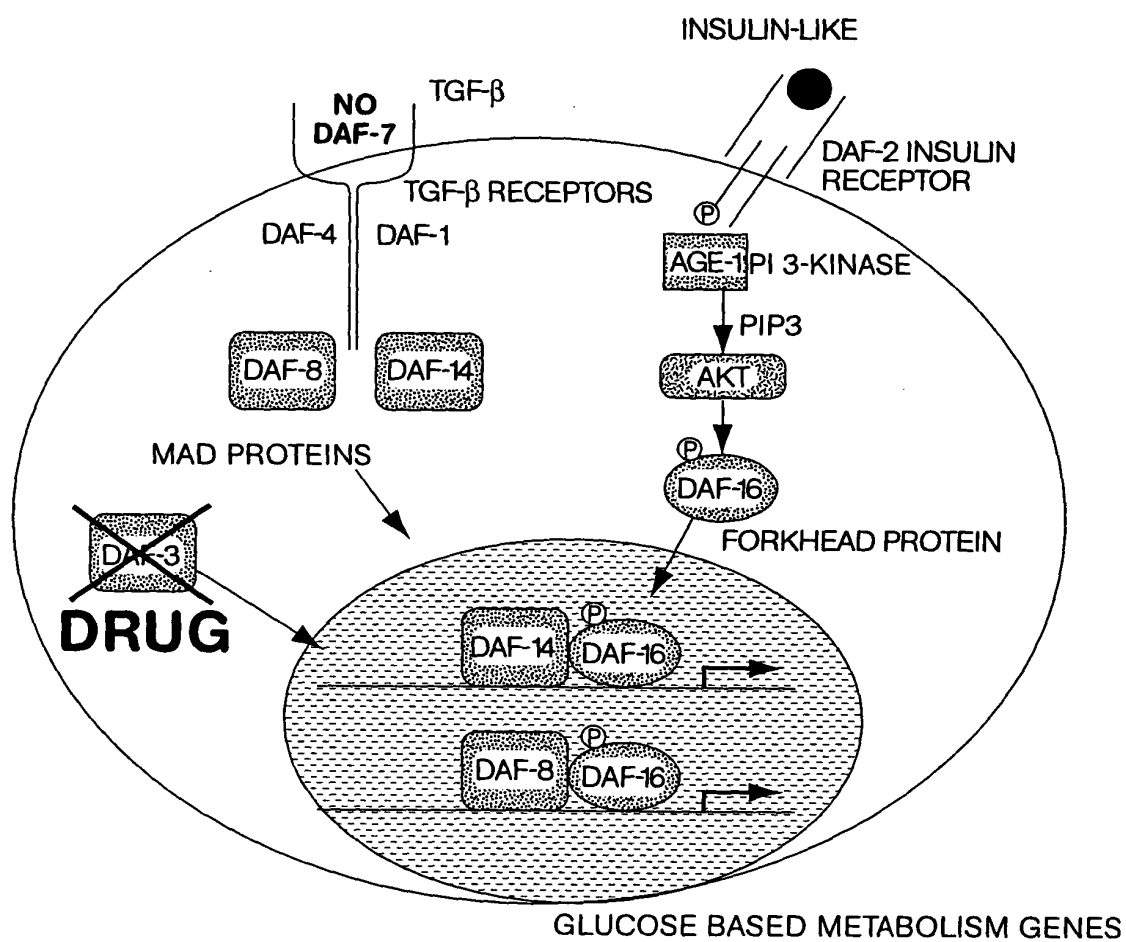
Fig. 20

```
Hnf3a              ..........  ..........  ..........  ..........  ..........  .........       0
Hnf3g              ..........  ..........  ..........  ..........  ..........  ........        0
D16123a467891011   MMEMLVDQGT  DASSSASTST  SSVSRFGADT  FMNTPDDDVMM .NDDMEPIPRD  RCNTW          55
D161256 7891011    MMEMLVDQGT  DASSSASTST  SSVSRFGADT  FMNTPDDDVMM .NDDMEPIPRD  RCNTW          55
Afx                ....MRIQ    PQKAAAIIDL  DPDFEPQSRP  RSCTW                                   29
Fkhr               MAEAPQVVEI  DPDFEPLPRP  RSCTW                                               25
Consensus          ----------  ----------  --------D-  EP--R---TW                             55

Hnf3a              ....MLGT    VKMEGHETSD  WNSYYADTQE  EYSSVPVSNM  NSGLG                        39
Hnf3g              ....MLGS    VKMEAHDLAE  W.SYYPEAGE  VYSPV....   .TPVP                        32
D16123a467891011   PMRRPQLEPP  LNSSPIIHEQ  IPEEDADLYG  SNEQCGQLGG  ASSNGSTAML  HTPDG          110
D161256 7891011    PMRRPQLEPP  LNSSPIIHEQ  IPEEDADLYG  SNEQCGQLGG  ASSNGSTAML  HTPDG          110
Afx                PLPRPEI     QPSEPPEVEP  DLGEK                                               53
Fkhr               PLPREF      AN.....     APSGSAAANP  DAAAG                                   57
Consensus          P--RP-----  -------E--  ----A-S---  -G                                     110

Hnf3a              SMNSMNTYMT  MNTMTTSGNM  TPASFNMSYA  NPALGAGLSP                               79
Hnf3g              TMAPLNSYMT  LNPLSSP...  YPGGLP...A  SPLPSGPLAP                               66
D16123a467891011   SNSHQTSFPS  D.........                                                    121
D161256 7891011    SNSHQTSFPS  ECYTWPMQQY  IYQESSATIP  HHHLNQHNNP  YHPMHPHHQL  PHMQQ          165
Afx                VHT.......                                                                  56
Fkhr               LPSASAAAVS  ADFMS.....                                                      72
Consensus          ----------  ----------  ----------  ----------                             165

Hnf3a              ........G   AVAGMPGGSA  GAMNSMTAAG  VTAMGTALSP  SGMGAMGAQQ  AASMM          125
Hnf3g              ........P   APAAPLGPTF  PGL.......  ..GLSGGGSS  SGYGAPGP..                  96
D16123a467891011   LPQPLLNLNM  TTLTSSGSSV  ASSIGGGAQC  SPCASGSSTA  ATNSSQQQQT  VGQML          121
D161256 7891011                                                                              220
Afx                ......NL    SLLEESEDFP  QAPGSVAAAV  AAAAAAAATG  .EGRS  EPILL                65
Fkhr                                                              GLCGDFQGPE  AGCLH          119
Consensus          ----------  ----------  ----------  ----------  ----------  -              220

Hnf3a              NGLGPYAAAM  NPCMSPMAYA  PSNLGRSRAG  GGGDAKTFKR  SY...PHAKP  PYSYI          177
Hnf3g                                                 GLVHGKEMPK  GYRAPAHAKP  PYSYI          121
D16123a467891011   .....FRMS   ESPDDTVSGK  K.........  .TTRRNAWG   NMSYA                      150
D161256 7891011    AASVPCSSSG  MTLGMSLNLS  QGGGMPAKK   KRCRKKPTDQ  LAQKKPNPWG  EESYS          275
Afx                PSRLSEPAGG  P...QPGILG  AVTGP.....  .RK......   .GGSRRNAWG  NQSYA          103
Fkhr               PAPPQPPPPG  PVSQHPPVPP  AAAGPLAGQP  RKS.......  .SSSRRNAWG  NLSYA          166
Consensus          ----------  ----------  ----------  ----------  ----------  -SY- NAWG      275
```

Fig. 21A (sheet 1 of 3)

Fig. 21A (sheet 2 of 3)

```
                    GSTLPASLPL GSASVTTRSP IEPSALEPAY YQGVYSRPVL NTS........ ........... 473
Hnf3a
Hnf3g               GAE....... .......... .GGEPGVY.. YQGLYSRSL. NAS........ ........... 347
D16123a467891011    .....SDIVD RTDQMRIDAT THIGGVQ... .IKQESKPIK TEPIAPPPSY HELNS....... 397
D16125567891011     .....SDIVD RTDQMRIDAT THIGGVQ..: .IKQESKPIK TEPIAPPPSY HELNS....... 522
Afx                 SSSLFSP... ....AE..... GPLSAGEGCF SSSQALEALL TSDTPPPPAD VLMTQ....... 381
Fkhr                GQSSMSPLPQ MPIQTLQDNK SSYGGMSQYN CAPGLLKELL TSDSPPH..N DIMTP....... 479
Consensus           ---------- --------S-- ---GG----- -------S--- -----P--H-- --T--------- 605

Hnf3a               .......... .......... .......... .......... .......... ........... 473
Hnf3g               .......... .......... .......... .......... .......... ........... 347
D16123a467891011    ..VRGSCAQNP .LERNPIVPS TNFKPMPLPG AYGNYQNGGI TPINWLSTSN SSPLP...... 450
D16125567891011     ..VRGSCAQNP .LERNPIVPS TNFKPMPLPG AYGNYQNGGI TPINWLSTSN SSPLP...... 575
Afx                 VDPILSQAPT .LLE...... .LGG...... LPSS..SKLA TGVGLC.... PKPLE...... 416
Fkhr                VDPGVAQPNS RVLGQNVMMG PNSVMSTYGS QASH..NKMM NPSSHTHPGH AQQTS...... 532
Consensus           V--------Q- ---Q------ ---E------ ---------- ---------- ----------- 660

Hnf3a               .......... .......... .......... .......... .......... ........... 473
Hnf3g               .......... .......... .......... .......... .......... ........... 347
D16123a467891011    ..GIQSCGIVAA QHTVASSSAL PIDLENLTLP DQPLMDTM.. .......... ........... 488
D16125567891011     ..GIQSCGIVAA QHTVASSSAL PIDLENLTLP DQPLMDTM.. .......... ........... 613
Afx                 ARGPSSLVPT LSMIAPPPVM AS........ .APIPKALGT PVLTPPTEAA S......... 458
Fkhr                AVNGRPLPHT VSTMPHTSGM NRLTQVKTPV QVPLPHPMQM SALGGYSSVS SCNGY....... 587
Consensus           ---------- ---------- ---------- --P------- ---------- -----------| 715

Hnf3a               .......... .......... .......... .......... .......... ........... 473
Hnf3g               .......... .......... .......... .......... .......... ........... 347
D16123a467891011    .......... ...DVDA... LIRHELSQAG GQHIHFDL.. .......... ........... 510
D16125567891011     .......... ...DVDA... LIRHELSQAG GQHIHFDL.. .......... ........... 635
Afx                 ...QDR MPQDLDLDMY MENLECDMDN IISDLMDEGE GLDFNFEPDP .......... 501
Fkhr                GRMGLLHQEK LPSDLD.GMF IERLDCDMES IIRNDLMDGD TLDFNEDNVL PNQSF...... 641
Consensus           ---------- ---------- ------D--- -----H---- ---------E- ----------| 770

Hnf3a               .......... .......... 473
Hnf3g               .......... .......... 347
D16123a467891011    .......... .......... 510
D16125567891011     .......... .......... 635
Afx                 .......... .......... 501
Fkhr                PHSVKTTTHS WVSG...... 655
Consensus           ---------- ----------| 784
```

Fig. 21A (sheet 3 of 3)

Fig. 21B

intestine   muscle

hypodermis

daf-16:GFP
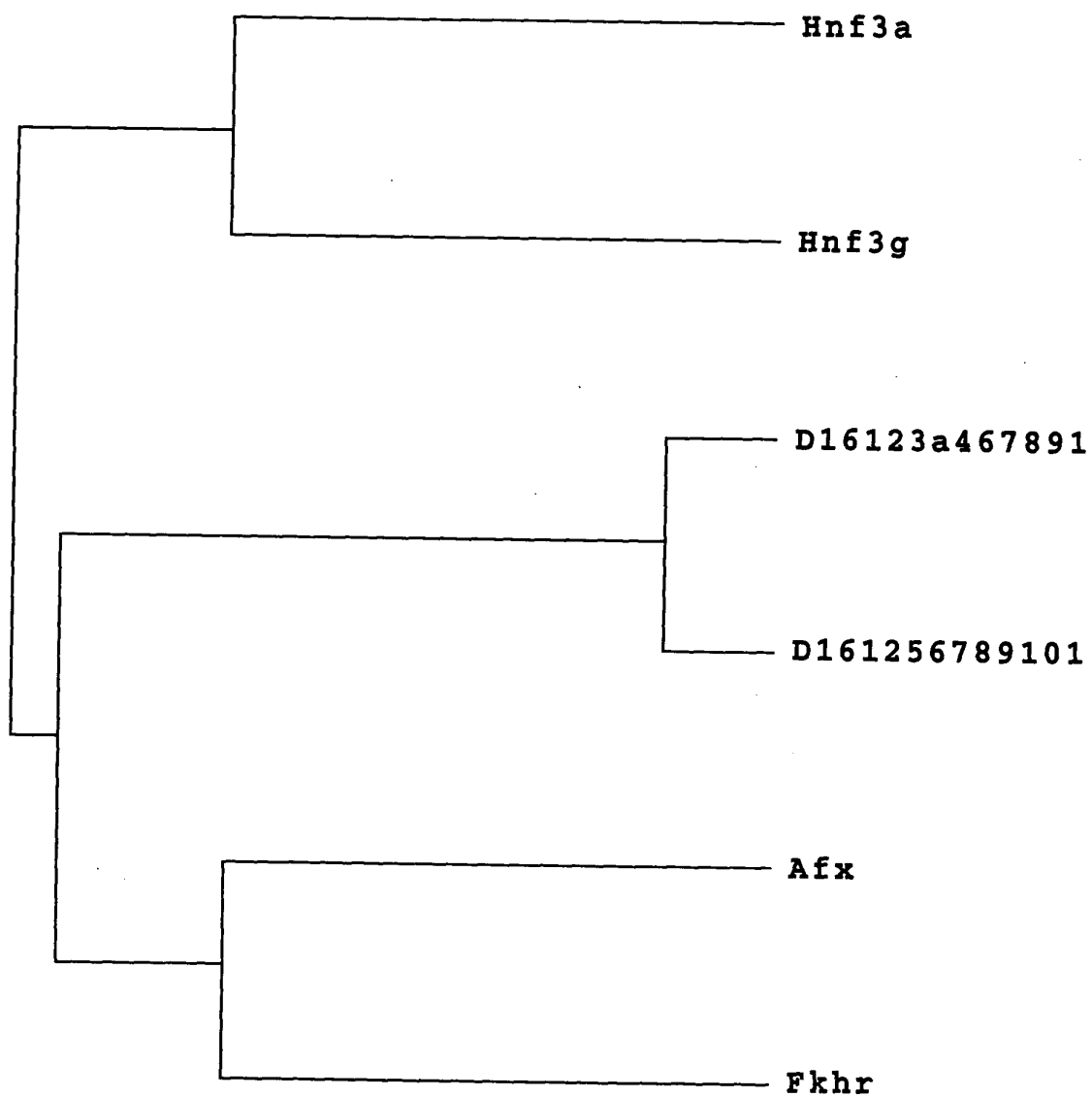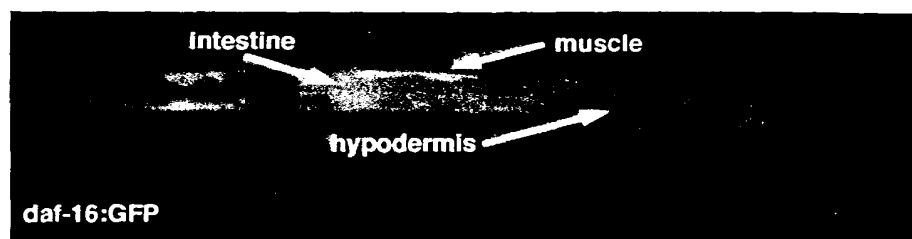
Fig. 22

INJECTION OF OF DAF-7 BYPASSES OBESITY-INDUCED DEFECTS IN INSULIN-REGULATION OF METABOLISM

DAF-7 PRODUCTION IS FAT-REPRESSED

DAF-7 ⊣

HYPOTHALAMUS?
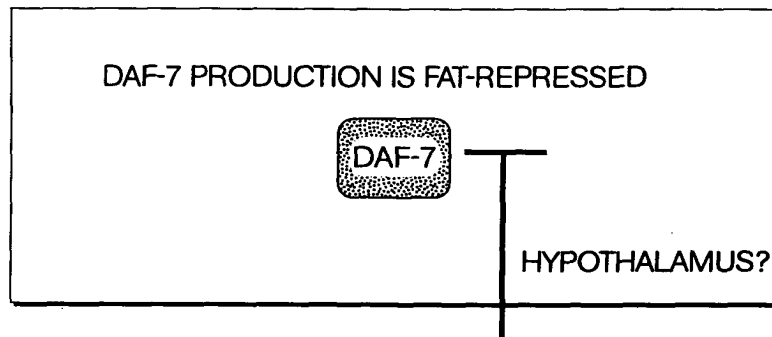
FATTY ACIDS IN BLOOD REPRESS DAF-7 IN ANALOGY TO PHEROMONE REGULATION OF DAF-7 IN C. ELEGANS

INSULIN-LIKE

DAF-7 DAF-7 DAF-7

TGF-β

DAF-7

DAF-2 INSULIN RECEPTOR

TGF-β RECEPTORS

DAF-4 DAF-1

Ⓟ AGE-1 PI 3-KINASE

Ⓟ DAF-8 Ⓟ DAF-14

PIP3

AKT

MAD PROTEINS

Ⓟ DAF-16

FORKHEAD PROTEIN

DAF-3

Ⓟ DAF-14 DAF-3 Ⓟ DAF-16

Ⓟ DAF-8 DAF-3 Ⓟ DAF-16

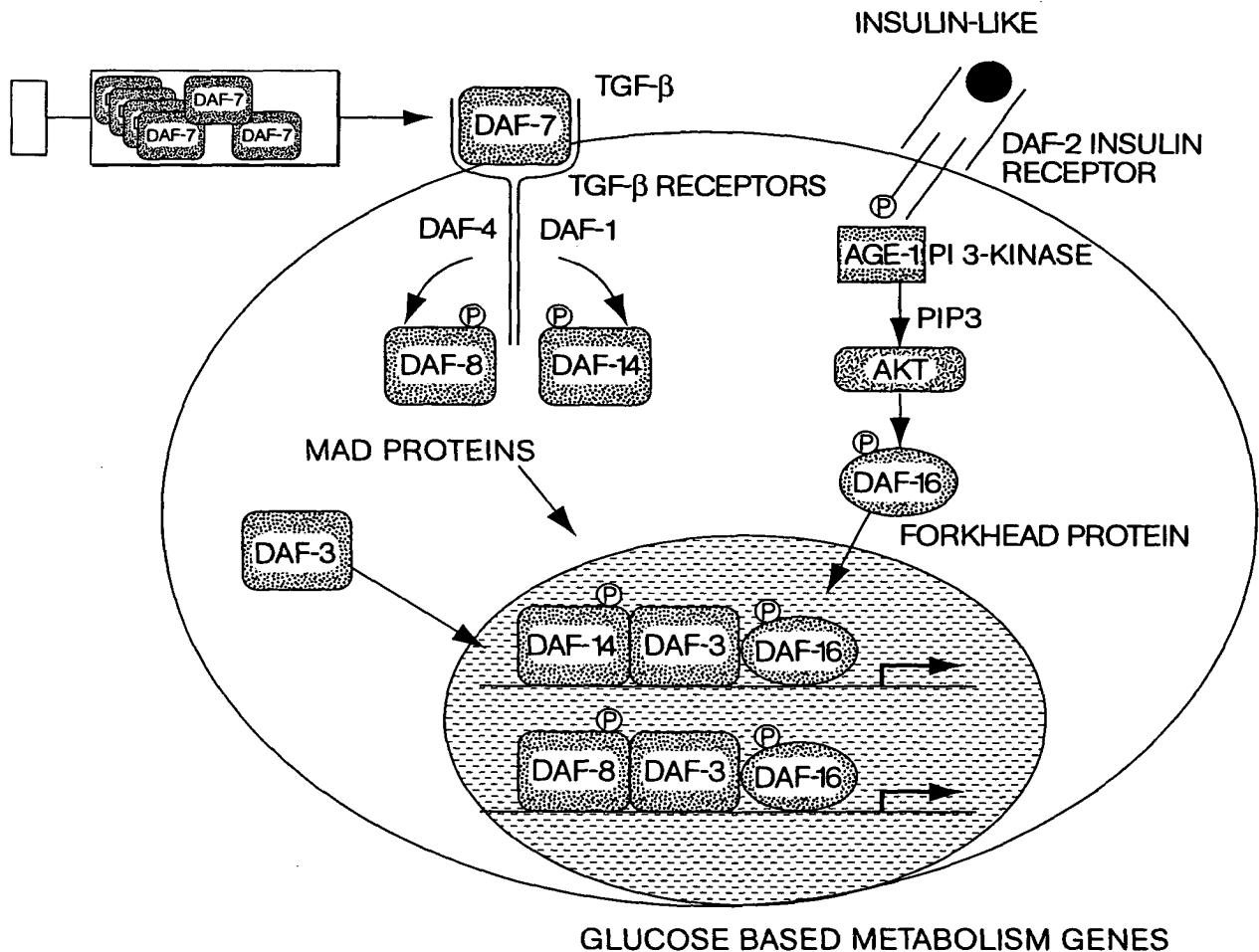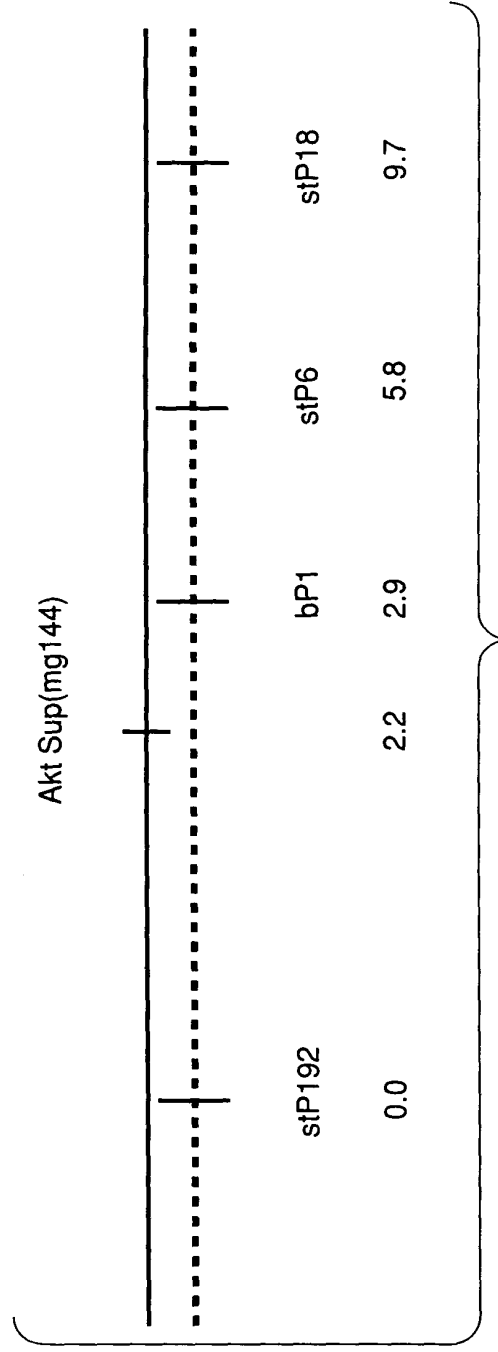GLUCOSE BASED METABOLISM GENES

Fig. 23

Fig. 24

Comparison of the human AKT protein sequence to the cosmid sequence
C12D8, located in the genetic interval where sup(mg144) maps. Numbering in the AKT
protein sequence by amino acid residues, and in the cosmid sequence by nucleotide
position.

```
Score = 450 (207.4 bits), Expect = 5.2e-165, Sum P(7) = 5.2e-165
Identities = 79/121 (65%), Positives = 97/121 (80%), Frame = +1

Query:    319 EVLEDNDYGRAVDWWGLGVVMYEMMCGRLPFYNQDHEKLFELILMEEIRFPRTLGPEAKS 378
                +VL+D+DYGR VDWWG+GVVMYEMMCGRLPFY++DH KLFELI+  ++RFP  L  EA++
Sbjct:  33685 QVLDDHDYGRCVDWWGVGVVMYEMMCGRLPFYSKDHNKLFELIMAGDLRFPSKLSQEART 33864

Query:    379 LLSGLLKKDPTQRLGGGSEDAKEIMQHRFFANIVWQDVYEKKLSPPFKPQVTSETDTRYFD 439
                LL+GLL KDPTQRLGGG EDA EI +  FF  + W+  Y K++ PP+KP V SETDT YFD
Sbjct:  33865 LLTGLLVKDPTQRLGGGPEDALEICRADFFRTVDWEATYRKEIEPPYKPNVQSETDTSYFD 34047


Score = 256 (118.0 bits), Expect = 5.2e-165, Sum P(7) = 5.2e-165
Identities = 48/66 (72%), Positives = 59/66 (89%), Frame = +1

Query:    146 TMNEFEYLKLLGKGTFGKVILVKEKATGRYYAMKILKKEVIVAKDEVAHTLTENRVLQNS 205
                TM +F++LK+LGKGTFGKVIL KEK T + YA+KILKK+VI+A++EVAHTLTENRVLQ
Sbjct:  32314 TMEDFDFLKVLGKGTFGKVILCKEKRTQKLYAIKILKKDVIIAREEVAHTLTENRVLQRC 32493


Query:    206 RHPFLT 211
                +HPFLT
Sbjct:  32494 KHPFLT 32511


Score = 190 (87.6 bits), Expect = 5.2e-165, Sum P(7) = 5.2e-165
Identities = 36/45 (80%), Positives = 37/45 (82%), Frame = +2

Query:    276 KLENLMLDKDGHIKITDFGLCKEGIKDGATMKTFCGTPEYLAPEV 320
                KLENL+LDKDGHIKI DFGLCKE I G    TFCGTPEYLAPEV
Sbjct:  33509 KLENLLLDKDGHIKIADFGLCKEEISFGDKTSTFCGTPEYLAPEV 33643


Score = 188 (86.7 bits), Expect = 5.2e-165, Sum P(7) = 5.2e-165
Identities = 37/57 (64%), Positives = 42/57 (73%), Frame = +3

Query:    209 FLTALKYSFQTHDRLCFVMEYANGGELFFHLSRERVFSEDRARFYGAEIVSALDYLH 265
                +   LKYSFQ   LCFVM+++ANGGELF H+ +   FSE RARFYGAEIV AL YLH
Sbjct:  32667 YFQELKYSFQEQHYLCFVMQFANGGELFTHVRKCGTFSEPRARFYGAEIVLALGYLH 32837


Score = 166 (76.5 bits), Expect = 5.2e-165, Sum P(7) = 5.2e-165
Identities = 29/59 (49%), Positives = 42/59 (71%), Frame = +1

Query:     53 NNFSVAQCQLMKTERPRPNTFIIRCLQWTTVIERTFHVETPEEREEWATAIQTVADGLK 111
                +  F++   Q M E+PRPN F++RCLQWTTVIERTF+ E+ E R+ W  AI++++   K
Sbjct:  31846 STFAIFYFQTMLFEKPRPNMFMVRCLQWTTVIERTFYAESAEVRQRWIHAIESISKKYK 32022


Score = 134 (61.8 bits), Expect = 5.2e-167, Sum P(8) = 5.2e-167
Identities = 24/33 (72%), Positives = 30/33 (90%), Frame = +3

Query:    210 LTALKYSFQTHDRLCFVMEYANGGELFFHLSRE 242
                L  LKYSFQT+DRLCFVME+A GG+L++HL+RE
Sbjct:  33156 LQELKYSFQTNDRLCFVMEFAIGGDLYYHLNRE 33254
```
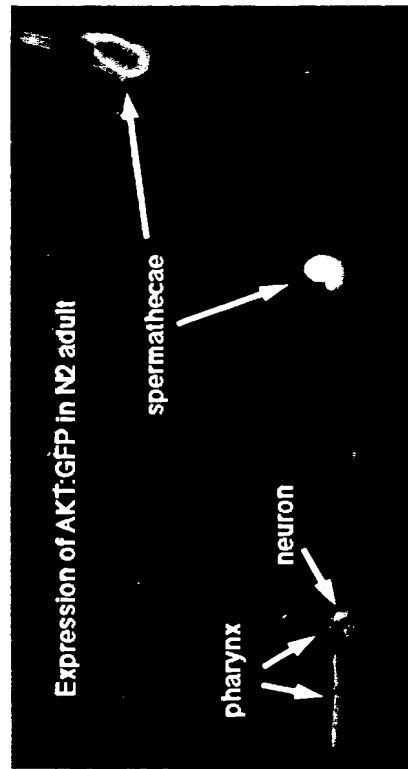
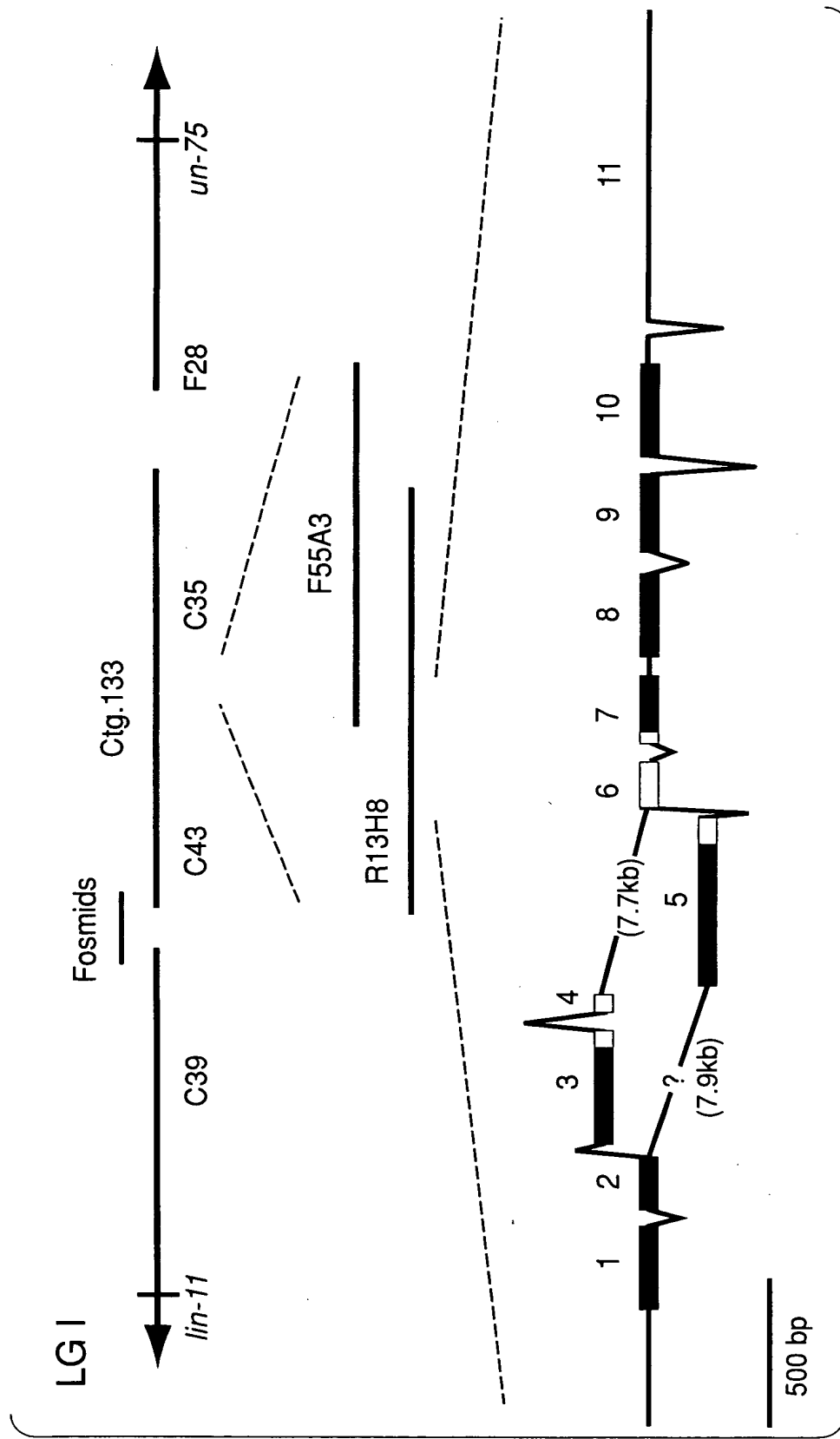Fig. 25

Expression of AKT:GFP in daf-2 dauers

Fig. 26A

Expression of AKT:GFP in N2 adult

pharynx

neuron

spermathecae

Fig. 26B

Fig. 27